Carboxylate-Assisted Ruthenium(II)-Catalyzed C−H Alkylation and Alkenylation

Dissertation

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Contents

Abbreviations

Ac	Acetyl
Ad	Adamantyl
Alk	Alkyl
AMLA	Ambiphilic metal-ligand activation
aq.	aqueous
Ar	Aryl
atm	Atmosphere
9-BBN	9-Borabicyclo[3.3.1]nonan
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bpy	2,2'-Bipyridine
Bu	Butyl
cat.	Catalytic
CMD	Concerted metalation-deprotonation
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
dba	Dibenzylidenaceton
DCE	1,2-Dichloroethane
DG	Directing group
diglyme	Diglycol methyl ether
DMA	*N,N*-Dimethylacetamide
DMAP	4-(Dimethylamino)-pyridin
DME	1,2-Dimethoxyethane
DMEDA	*N*,*N*′-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DoM	Directed *ortho*-metalation
EI	Electron ionization
ESI	Electronspray ionization
Et	Ethyl
EWG	Electron withdrawing group
FTICR	Fourier transform ion cyclotron resonance
GC-MS	Gas transform ion cyclotron resonance
gem	Geminal
h	Hour
Hex	Hexyl

HMDS	Hexamethyldisilazan
HR-MS	High resolution mass spectrometry
IES	Internal electrophilic substitution
i-Pr	*iso*-Propyl
IR	Infrared
LDA	Lithiumdiisopropylamid
M	Metal
Mes	2,4,6-Trimethylphenyl
Me	Methyl
m	*meta*
mol.	Molecular
M.p.	Melting point
M.r.	Melting range
NMP	*N*-Methyl-2-pyrrolidone
o	*ortho*
p	*para*
cymene	4-*iso*-Propyltoluene
PEG	Polyethylene glycol
Pent.	Pentyl
Phen.	Phenanthroline
Ph	Phenyl
Piv	Pivalyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
S_EAr	Electrophilic aromatc substitution
SPO	Secondary phosphine oxid
T	Temperature
t-Am	*tert*-Amyl
Tf	Triflouromethanesulfonyl
TFA	Triflouroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Transition metal
TMS	Trimethylsilyl
TS	Transition state
UV	Ultraviolet
X	Halide

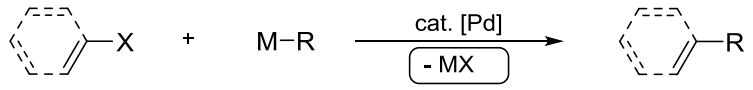
1 Introduction

Sustainability is important, because our natural sources are limited and our environment needs protection. Organic chemistry has to face this challenge.

Thus, one of the major goals of sustainable chemistry is the site- and chemo-selective synthesis of organic compounds, without side-products and waste, in a step-economical fashion under mild reaction conditions.

During the last decades, progress has been made in the important field of C−C bond formations.[1] The transition metal-catalyzed cross-coupling reactions,[2] forming chemo- and site-selective C−C bonds, were developed by several research groups.[3] Because of their pioneering work *Heck*, *Negishi* and *Suzuki* were awarded with the *Nobel* prize in chemistry in 2010, thus illustrating the importance of this methodology.[4]

The traditional cross coupling reaction is presented in Scheme 1.1.



1 **2** **3**

Scheme 1.1: Traditional cross-coupling reaction.

In general, an aryl, alkenyl or alkyl (pseudo)halide reacts as an electrophile with an organometallic reagent as a nucleophile *via* transition metal catalysis. The key features of the mechanism of cross-coupling reactions are the oxidative addition of the (pseudo)halide to the active catalyst, the transmetalation with the organometallic reagent and the subsequent reductive elimination to give the coupled product. In the *Mizoroki-Heck* reaction the product is formed *via syn*-insertion, followed by *σ*-bond rotation and *β*-hydride elimination.[5] Because of the use of prefunctionalized starting materials and the stoichiometric amounts of metal salts produced as side products this transformation is not ideal. To avoid the disadvantages of the

[1] (a) A. Behr, *Angewandte homogene Katalyse*, Wiley-VCH, Weinheim, **2008**; (b) *Modern Arylation Methods*, (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**; (c) G. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564; (d) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

[2] (a) C. C. C. Johansson Seechurn, M. O. Kitching, T.J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5086. (b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds. de Meijere, A.; Diederich, F.), 2nd ed., Wiley-VCH: Weinheim, **2004**. (c) *Transition Metals for Organic Synthesis* (Eds. Beller, M.; Bolm, C.), 2nd ed., Wiley-VCH: Weinheim, **2004**.

[3] For recent reviews on conventional cross-coupling reactions, see: (a) *Chem. Soc. Rev*. **2011**, *40*, Special Issue 10 *"Cross coupling reactions in organic synthesis"*, 4877–5208; (b) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; (c) G. Cahiez, A. Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435–1462.

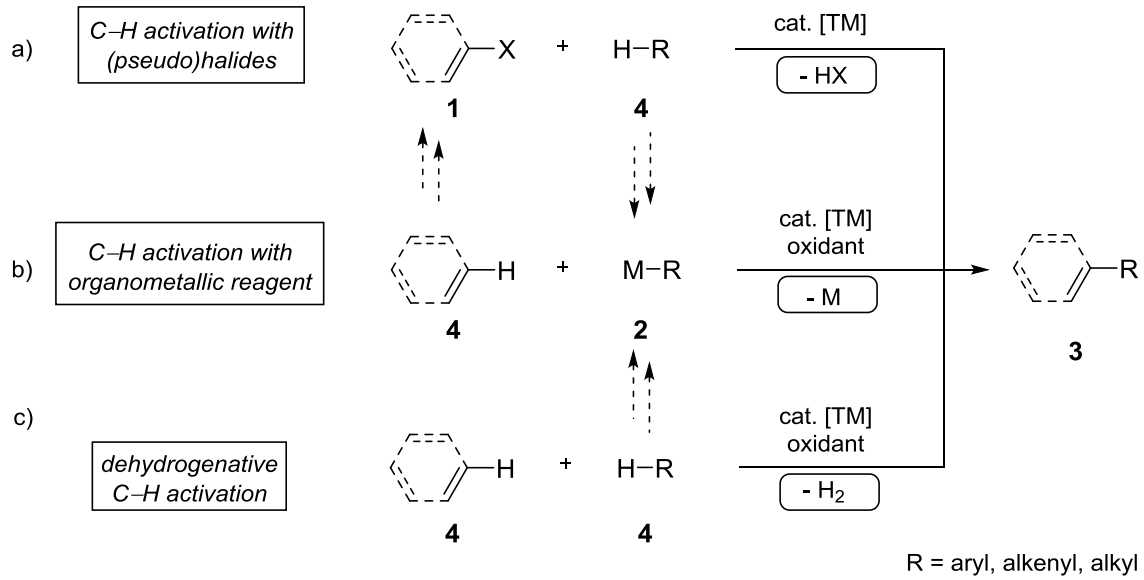
[4] "The Nobel Prize in Chemistry 2010 - Press Release". Nobelprize.org. Nobel Media AB 2013. Web. 25 Feb. 2014. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/press.html

[5] J. P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.

cross-coupling reactions several research groups studied the transition metal-catalyzed direct functionalization of C−H bonds.[6]

1.1 Transition Metal Catalyzed C−H Bond Functionalization

Unlike traditional cross-coupling reactions, direct C−H bond functionalizations[6] have the advantage that prefunctionalized starting materials are not needed. Scheme 1.2 shows three different strategies for transition metal-catalyzed direct C−H bond functionalizations.[7]



Scheme 1.2: Strategies for transition metal-catalyzed C−H bond functionalization

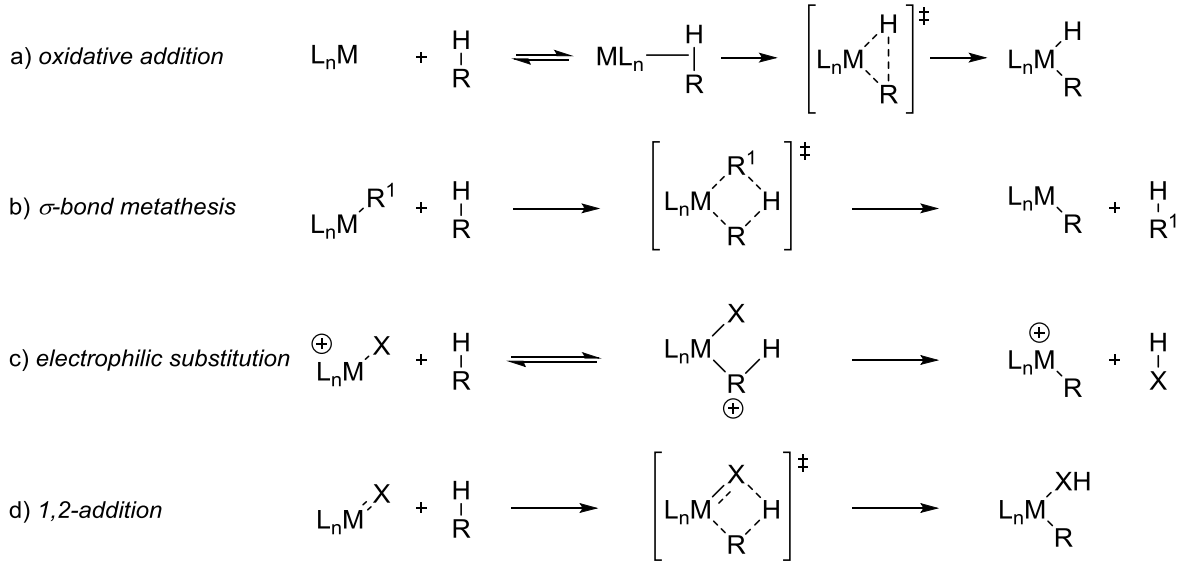
In reference to traditional cross-coupling reactions, Scheme 1.2 a presents the coupling of aryl or alkenyl substrates with an unactivated C−H bond and aryl or alkenyl (pseudo)halides. In contrast, the reaction in Scheme 1.2 b displays the coupling between arenes or alkenes with organometallic reagents. The last strategy demonstrates the dehydrogenative coupling by activation of two C−H bonds (Scheme 1.2 c). For the latter two transformations,

[6] For recent reviews on C–H bond functionalizations, see (a) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal*. **2014**, *356*, 1461–1479; (b) K. Gao, N. Yoshikai, *Acc. Chem. Res*. **2014**, *47*, 1208−1219; (c) B. Li, P. H. Dixneuf, *Chem. Soc. Rev*. **2013**, *42*, 5744–5767; (d) T. A. Ramirez, B. G. Zhao, Y. Shi, *Chem. Soc. Rev*. **2012**, *41*, 931–942; (e) Z.-Z. Shi, C. Zhang, C.-H. Tang, N. Jiao, *Chem. Soc. Rev*. **2012**, *41*, 3381–3430; (f) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814–825; (g) J. L. Bras, J. Muzart, *Chem. Rev*. **2011**, *111*, 1170–1214; (h) L. Ackermann, *Chem. Comm.* **2010**, *46*, 4866-4877; (i) T.W. Lyons, M. S. Sanford, *Chem. Rev*. **2010**, *110*, 1147–1169; (j) A. A. Kulkarni, O. Daugulis, *Synthesis,* **2009**, 4087–4109; (k) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev*. **2009**, *38*, 3242–3272; (l) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu. *Angew. Chem. Int. Ed*. **2009**, *48*, 5094–5115. For reports on atom- and step-economy, see: (m) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; (n) B. M. Trost, *Science,* **1991**, *254*, 1471–1477; (o) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res*. **2008**, *41*, 40–49.

[7] L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826.

stoichiometric amounts of oxidants are essential. While the two first strategies still need at least some prefunctional starting materials, the dehydrogenative coupling is the most step- and atom-economical reaction, as it does not require any prefunctionalized starting materials. This is in accordance with the concept of green chemistry.[8]

The transition metal-catalyzed C−H bond functionalization emerged also from the concept of green chemistry. The C−H bond functionalizations could be carried out chemo-, site-, and enantioselectively with a variety of transition metals such as palladium,[6g,6k,6l] ruthenium,[6a,6c] rhodium,[6f] cobalt[6b,6j] and nickel.[6j] The varieties of these reactions lead to intensive investigations of the catalyst´s working mode. As a consequence, four generally accepted mechanistic pathways[9] for the C−H bond metalation step were postulated (Scheme 1.3). Computational studies of these mechanisms were summarized by *Eisenstein* and co-workers.[10]

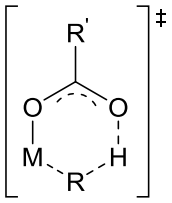


Scheme 1.3: Possible mechanisms for C−H bond metalation by transition metal complexes.[8c]

The first pathway considered, is the oxidative addition (Scheme 1.3 a), which can be performed by electron rich and low-valent complexes of late transition metals. Whereas early transition metals with d^0-configuration cannot undergo oxidative addition, *σ*-bond metathesis (Scheme 1.3 b) takes usually place here. While electrophilic substitution (Scheme 1.3 c) occurs with electron deficient late transition metals, alkylidene or imido complexes of early transition metals display the possibility of C−H activation *via* 1,2-additions (Scheme 1.3 d).

[8] Ackermann, L.; Kapdi, A. R.; Potukuchi, H. K.; Kozhushkov, S. I. In Handbook of Green Chemistry (Ed. Li, C.-J.), Wiley-VCH: Weinheim, 2012, 259–305.
[9] (a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831; (b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.
[10] D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749–823.

New developments display a bifunctional process, which involves C−H activation by an electrophilic metal working synergistically with secondary phosphine oxides or carboxylates. Six membered transition states are formed during this mechanism, which was coined as CMD[11] (concerted-metalation-deprotonation) or AMLA[9a] (ambiphilic metal-ligand activation) (Scheme 1.4).



CMD/AMLA TS

Scheme 1.4: Proposed transition states for the CMD/AMLA activation.

These mechanistical investigations are the foundation of the transition metal-catalyzed C−H bond functionalization, which has gained a lot of attention in recent years and is used for the catalyzed synthesis of biaryls.[1b, 12] Transition metals used in C−H bond functionalization are relatively expensive. The prices of gold, platinum, rhodium, palladium, iridium and ruthenium are 1174, 1084, 900, 671, 550 and 45 US$ per troy oz, respectively.[13]

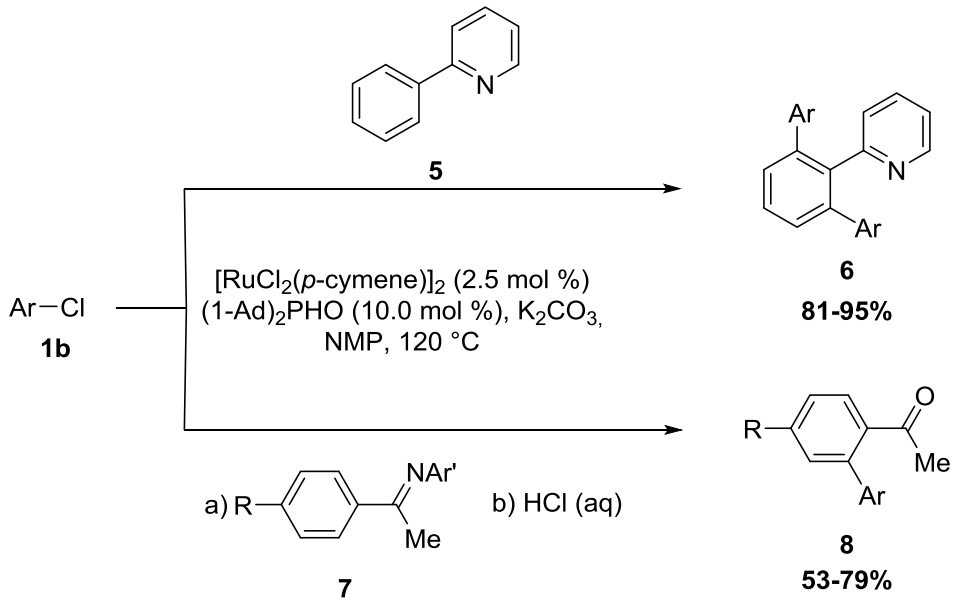
Ruthenium, a relatively inexpensive transition metal, proved to be broadly applicable in the C−H bond functionalization. Early studies on chelation-assisted ruthenium(II)-catalyzed direct arylations were performed by the *Ackermann* group in 2005. The ruthenium-catalyzed arylation of aryl pyridines or aromatic imines with easily accessible aryl chlorides proceeded with excellent chemo- and site-selectivity. This reaction featured a notable functional group tolerance and an excellent catalytic activity (Scheme 1.5).[14]

[11] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

[12] Selected reviews: (a) L. Ackermann, A. R. Kapdi, H. K. Potukuchi, S. I. Kozhushkov, In *Handbook of Green Chemistry* (Ed. Li, C.-J.), Wiley-VCH: Weinheim, **2012**, 259–305; (b) A. A. Kulkarni, O. Daugulis, *Synthesis,* **2009**, 4087–4109; (c) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; (d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; (e) F. Bellina, R. Rossi, *Chem. Rev.* **2010,** *110,* 1082–1146; (f) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; (g) T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res*. **2012**, *45*, 826–839; (h) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev*. **2011**, *40*, 5068–5083.

[13] Price metals https://www.quandl.com/collections/markets/palladium 1. 7. 2015.

[14] L. Ackermann, *Org. Lett.* **2005**, *7*, 3123−3125.



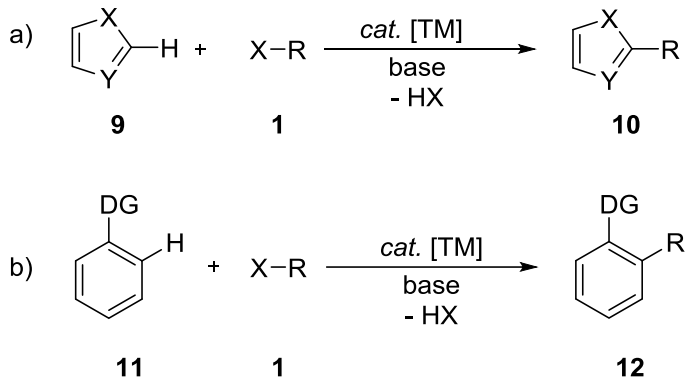
Scheme 1.5: Ruthenium-catalyzed arylations with aryl chlorides.[14]

Inspired by this inexpensive catalytic system the group of Prof. *Ackermann* focused on ruthenium(II)-catalyzed C−H bond functionalization. An extensive screening of different additives for ruthenium(II)-catalyzed arylations of aryl triazoles identified hindered carboxylic acids to be excellent ligands.[15] As can be seen in the previous example of ruthenium(II)-catalyzed arylation reaction, the site-selectivity is of great importance in C−H bond activation and remains a challenging issue.

1.2 Site-Selectivity

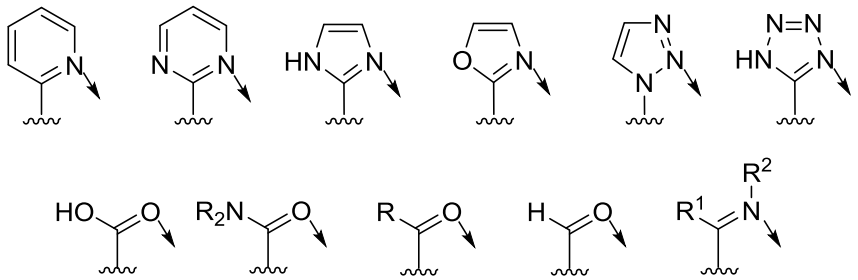
In particular site-selectivity was either obtained by enhanced acidity of a specific (hetero)aromatic C−H bond or by a *Lewis* basic directing group for the conversion of substrates into *ortho*-functionalized derivatives (Scheme 1.6).[16]

[15] (a) L. Ackermann, M. Mulzer, *Org. Lett.* **2008**, *10*, 5043–5045; (b) L. Ackermann, R. Born, R. Vicente, *ChemSusChem,* **2009**, 546–549; (c) L. Ackermann, R. Vicente, A. Althammer, *Org. Lett*. **2008**, *10*, 2299–2302.
[16] (a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010,** *110,* 624–655; (b) For a review on removable directing groups (DG) see: C. Wang, Y. Huang, *Synlett,* **2013**, *24*, 145–149.



Scheme 1.6: Two strategies for site-selective C−H bond functionalization

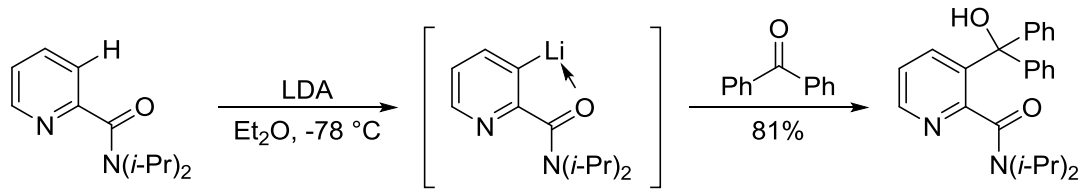
In both cases stoichiometric amounts of bases are necessary. The latter is the most common approach in direct C−H bond activation. The directing group contains a heteroatom with a lone pair of electrons that coordinates to the transition metal. During the last years, several heteroatom bearing directing groups (Scheme 1.7) have been introduced in palladium-, nickel-, rhodium-, ruthenium-, or iridium-catalyzed C−C bond formation.[7, 6h, 17]



Scheme 1.7: Directing groups in transition metal catalyzed C−C bond formation.

The directed *ortho*-metalation (DoM) mandates a similar approach, however using stoichiometric amounts of main group metals.[18] This concept was initially developed by *Gilman*[19] and *Wittig*[20] utilizing organolithium compounds (Scheme 1.8) and was extensively investigated by *Snieckus*.[21]

[17] (a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; (b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936–946; (c) S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886–896.
[18] J. P. Fleming, M. B. Berry, J. M. Brown, *Org. Biomol. Chem.* **2008**, *6*, 1215–1221.
[19] Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* **1939**, 61, 109–112.
[20] B. G. Hashiguchi, S. M. Bischof, M. M. Konnick, R. A. Periana, *Acc. Chem. Res.* **2012**, *45*, 885–898.
[21] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.



13 **14** **15**

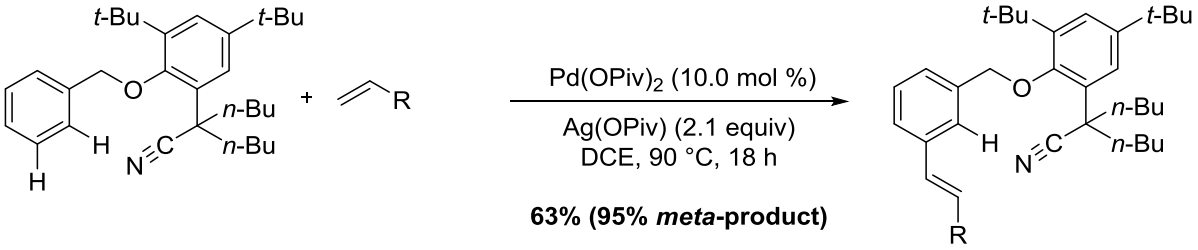
Scheme 1.8: DoM of a pyridine derivative.[22]

A great disadvantage of this strategy is the formation of stoichiometric amounts of lithium salts, as by-products. Moreover, the limited functional group tolerance is a major drawback, which is due to the high reactivity of the strong bases.

However, *ortho*-functionalization could be achieved quite easily, while *meta*- and *para*-functionalization remained challenging. Recently, *Knochel* made some progress in *meta*- and *para*-selective functionalization, using stoichiometric amounts of organomagnesium compounds in combination with several directing groups.[23] Furthermore, *Brown* and co-workers developed a *meta*-selective substitution with organolithiums and sulfoxides as removable directing group.[18]

Nevertheless, because of the disadvantages of the stoichiometric DoM-type reactions, such as the stoichiometric use of strong bases and the removal of the directing group, they cannot be considered as step- or atom-economical.

In 2012, *Yu* and co-workers developed a *meta*-selective palladium-catalyzed direct alkenylation applying an end-on template (Scheme 1.9) with easily removable directing group.[24]



16 **17** **18**

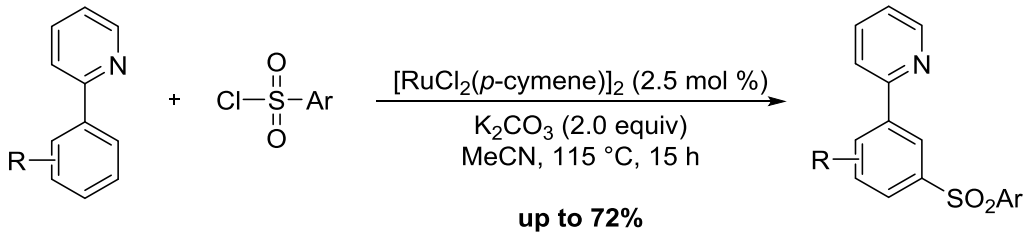
Scheme 1.9: Direct *meta*-alkenylation by *Yu*.[24]

Meta-selective reactions catalyzed by transition metals remained scarce. In 2009, the *Gaunt* group published a copper-catalyzed *meta*-arylation of anilides.[25] Shortly after this, the

[22] S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res*. **2012**, *45*, 936–946.
[23] (a) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503–1507; (b) G. Monzón, I. Tirotta, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 10624–10627.
[24] (a) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature,* **2012**, *486*, 518–522; (b) J. Li, S. De Sarkar, L. Ackermann, *Top. Organomet. Chem.* **2015**, DOI:10.1007/3418_2015_130.

research group published the *para*-selective arylation of phenols and anilines.[26] Both reactions were subsequently being shown to be *Brønsted*-acid-catalyzed transformations.

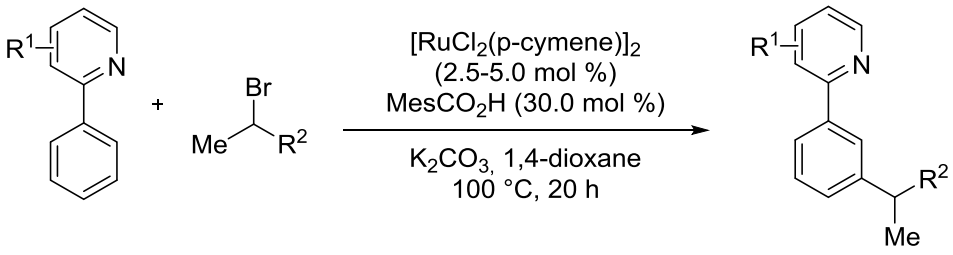
Ruthenium-catalyzed *meta*-selective C−H bond functionalizations are rare. *Frost* and co-workers reported the ruthenium-catalyzed *meta*-selective sulfonylation of 2-phenylpyridines (Scheme 1.10).[27] A drawback of the directing group is that it cannot be cleaved.



19 **20** **21**

Scheme 1.10: *Meta*-selective sulfonylation of 2-phenylpyridine reported by *Frost*.

Outstandingly, *Ackermann* and *co*-workers published the first ruthenium-catalyzed *meta*-selective alkylation of arenes (Scheme 1.11).[28]



22 **23** **24**

Scheme 1.11: *Meta*-selective C−H alkylation by *Ackermann*.

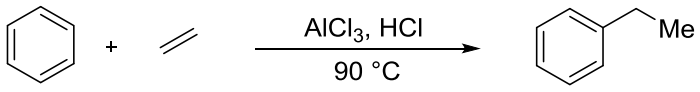
In spite of this example of *meta*-selectivity in alkylation reactions there is still a challenge, which has to be faced in the site-selective transition metal-catalyzed alkylation. In the past decade several research groups extensively investigated the site-selective alkylation reaction *via* C−H bond functionalization.[29]

[25] (a) R. J. Phipps, M. J. Gaunt, *Science,* **2009**, *323*, 1593–1597. For mechanistic DFT calculations, see: (b) S.-I. Zhang, Y. Ding, *Chin. J. Chem. Phys*. **2011**, *24*, 711–723; (c) B. Chen, X.-L. Hou, Y.-X. Li, Y.-D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668–7671.
[26] C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. Gaunt, *J. Angew. Chem. Int. Ed.* **2011**, *50*, 458–462.
[27] O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298–19301.
[28] N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877−5884.
[29] L. Ackermann, *Chem. Commun.* **2010***, 46*, 4866−4877.

1.3 Alkylation Reactions of Arenes

1.3.1 Friedel-Crafts Alkylation

The beginning of alkylation reaction was constituted by the *Friedel-Crafts* alkylation.[30] Untill today the reaction plays an important role and is employed on industrial scale. The synthesis of ethylbenzene from benzene and ethylene is arguably the largest C−C bond formation process used in industry (Scheme 1.12).[3]



4a **17a** **25**

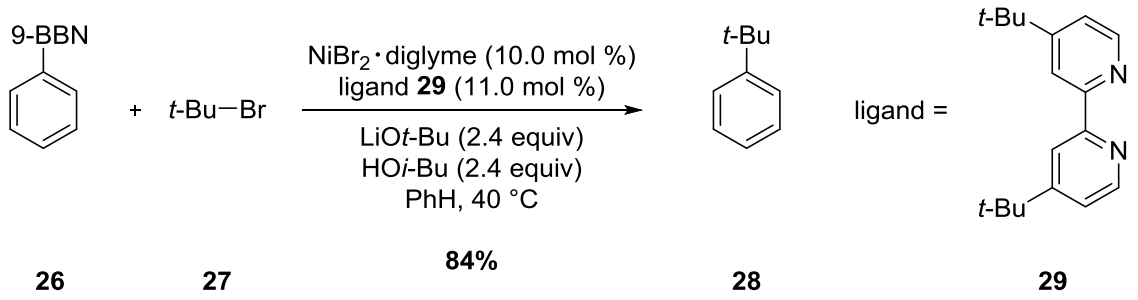
Scheme 1.12: *Friedel-Crafts* reaction of benzene **4a**.

Still this alkylation reactions face some disadvantages, which include the use of corrosive reagents, harsh reaction conditions and undesired side products. Besides these problems the reaction was continously impoved.[31]
An elegant solution to avoid the disadvatages of the *Friedel-Crafts* alkylation reaction is represented by the homogenous transition metal catalysis.

1.3.2 Cross-Coupling Reactions

Transition metal-catalyzed cross-coupling alkylating reactions are rare and have some difficulties when using unactivated alkyl (pseudo)halides. Two difficulties have to be faced in these reactions specifically for the alkyl halides. First, they process low reactivity, because of their electron-rich character. Second, they easily undergo *β*-hydride eliminations. Nevertheless, among this *Fu* demonstrated sucessfully the nickel-catalyzed *Suzuki-Miyaura* cross-coupling with tertiary alkyl halides (Scheme 1.13).[32]

[30] (a) C. Friedel, J. M. Crafts, *Compt. Rend*. **1877**, *84*, 1392–1450; (b) C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877,** *32,* 725–791.
[31] (a) M. Rüping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, 1–24; (b) T. Tsuchimoto, K. Tobita, T. Hiyama, S.-I. Fukuzawa, *Synlett,* **1996**, 557–559; (c) *Catalytic Asymmetric Friedel-Crafts Alkylations* (Eds.: Bandini, M.; Umani-Ronchi, A.), Wyley-VCH: Weinheim, 2009.
[32] S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135,* 624–627.

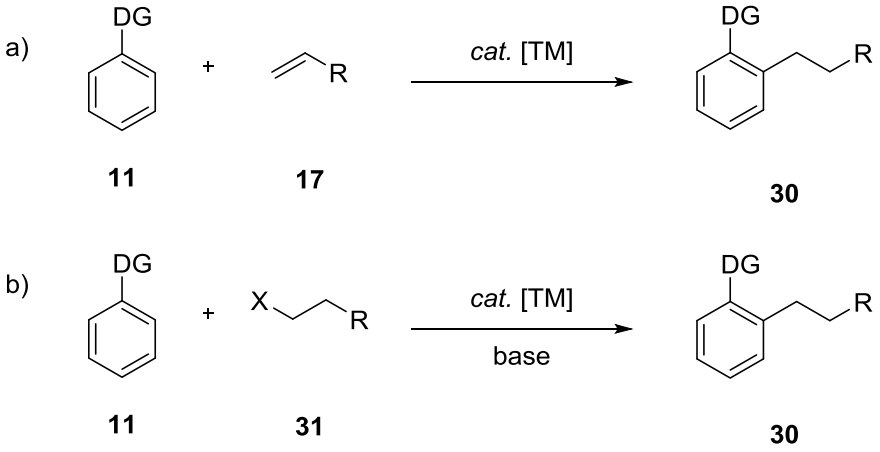


Scheme 1.13: Nickel-catalyzed cross-coupling of tert. alkyl halides.

Moreover, *Fu* put a lot of effort in the development of alkyl cross coupling reactions, which succeeded in the alkyl-alkyl *Negishi*[33] and *Suzuki-Miyaura*[34] couplings in recent years.
Despite these improvements the advantages of transition metal-catalyzed C−H bond functionalization dominate.

1.3.3 Transition Metal-Catalyzed C−H Bond Alkylation

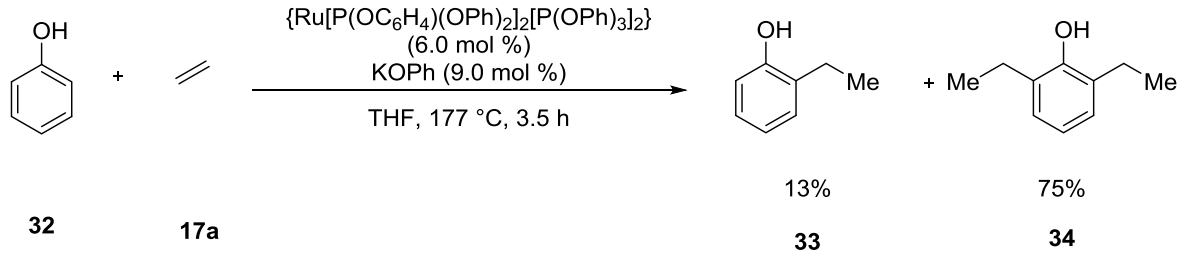
The transition metal-catalyzed C−H bond alkylation can be achieved by two different ways, namely the hydroarylation of alkenes (Scheme 1.14 a) and the alkylation with unactivated alkyl halides (Scheme 1.14 b).



Scheme 1.14: Transition metal-catalyzed alkylation.

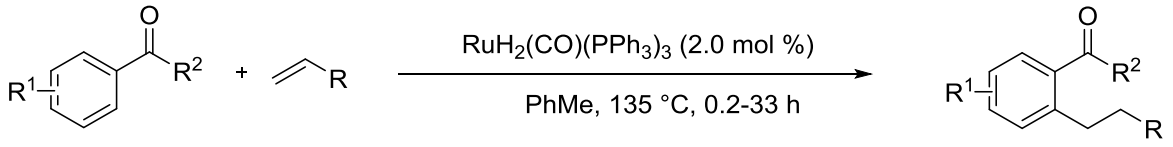
Pioneering work on the regioselective *ortho*-alkylation by hydroarylation of alkenes was done by *Lewis* and *Smith* in 1986 (Scheme 1.15).[35]

[33] (a) J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006. (b) J. Choi, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105. (c) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966–2969. (d) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647.
[34] (a) A. Wilsily, F. Tramutola, N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797. (b) S. L. Zultanski. G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 15362–15364. (c) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (d) S. Lu, G. C. Fu, *Angew Chem. In. Ed.* **2010**, *49*, 6676–6678. (e) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.
[35] A review: (a) L. N. Lewis, J. F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735; (b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918.



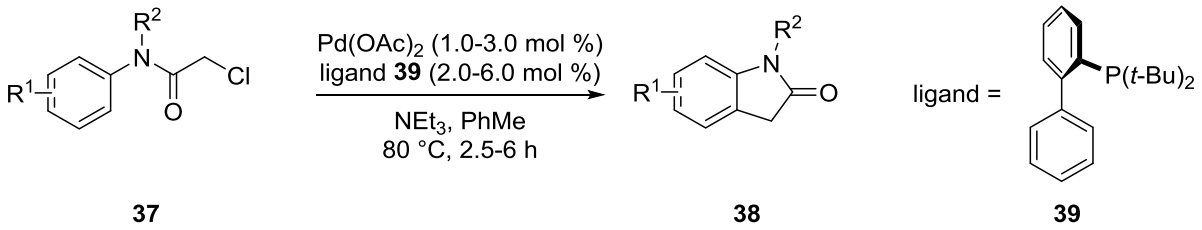
Scheme 1.15: Ruthenium(0)-catalyzed alkylation of phenol with ethylene.

The hyroarylation using ruthenium hydride complexes as catalysts was extended by *Murai*, *Chatani* and *Kakiuchi* in 1993[36] and is today known as the *Murai* reaction (Scheme 1.16). The main disadvantage of this reaction, the air sensitivity of the catalyst, could be solved by *Darses* and *Genet* using the *in situ* formed catalyst $[RuH_2(PPh)_3)_4]$.[37]



Scheme 1.16: Ruthenium(0)-catalyzed *Murai*-reaction.

An early example of the transition metal-catalyzed alkylation with alkyl (pseudo)halides was the palladium-catalyzed entropically-favored intramolecular direct alkylation for the synthesis of oxindoles **38** by *Hennessy* and *Buchwald* (Scheme 1.17).[38]



Scheme 1.17: Palladium-catalyzed intramolecular direct alkylation for the synthesis of oxindoles **40**.

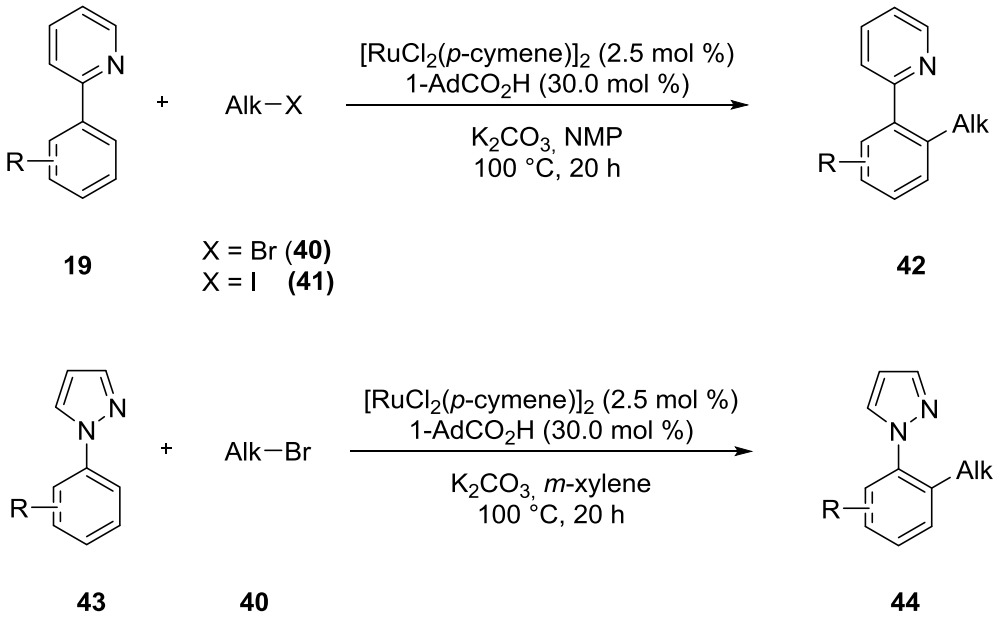
[36] (a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature,* **1993**, *366*, 529–531. (b) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834. For DFT-calculations, see: (c) U. Helmstedt, E. Clot, *Chem. Eur. J.* **2012**, *18*, 11449–11458. For ruthenium-catalyzed *Murai*-type carbonylations, see: (d) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *Org. Chem.* **1997**, *62*, 2604–2610.

[37] (a) R. Martinez, R. Chevalier, S. Darses, J.-P. Genet, *Angew. Chem. Int. Ed.* **2006**, *45*, 8232–8235; (b) R. Martinez, M.-O. Simon, R. Chevalier, C. Pautigny, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2009**, *131*, 7887–7895.

[38] E. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc*. **2003**, *125*, 12084–12085.

A number of nickel- and palladium-catalyzed alkylation reactions limited to heteroarenes were reported by *Hu,*[39] Ackermann[40] and *Miura* and *Satoh*.[41]

In spite of this challenging task, the transition metal-catalyzed direct *ortho*-alkylation with inexpensive ruthenium catalysts was achieved by *Ackermann* and co-workers. In 2009, *Ackermann* reported the ruthenium(II)-catalyzed C−H alkylation of arylpyridines with unactivated alkyl halides (Scheme 1.18). The scope was not limited to pyridines as directing group, but could be extended to pyrazoles and ketimines (Scheme 1.18).[42]



Scheme 1.18: Ruthenium(II)-catalyzed direct *ortho*-alkylation by *Ackermann*.

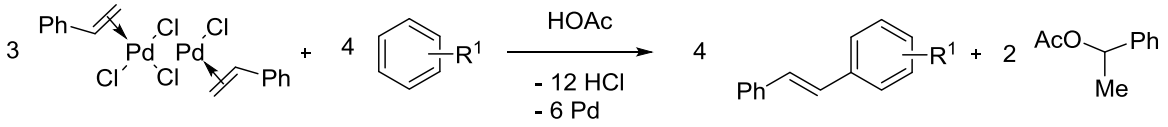
The benefits of the ruthenium(II)-catalyzed direct alkylations are that no *β*-hydride elimination of the alkyl halides takes place. Furthermore, inexpensive non prefunctionalized starting materials could be used. Fortunately, the inexpensive carboxylate-assisted catalytic system developed in the ruthenium(II)-catalyzed arylation reactions[15c] proved to be broadly applicable in the ruthenium-catalyzed alkylation. These outstanding site-selective C−C bond formations represent a further element in the transition metal-catalyzed C−H bond functionalization and therefore improved sustainability of organic chemistry.

[39] (a) P. Ren, I. Salihu, R. Scopelliti, X. Hu, *Org. Lett.* **2012**, *14*, 1748−1751; (b) O. Vechorkin, V. Proust, X. Hu, *Angew. Chem. Int. Ed.* **2010**, *49*, 3061−3064.
[40] L. Ackermann, B. Punji, W. Song, *Adv. Synth. Catal.* **2011***, 353*, 3325−3329.
[41] T. Yao, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 12307−12311.
[42] L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009***, 48*, 6045–6048.

1.4 Transition Metal-Catalyzed C−H Bond Alkenylation

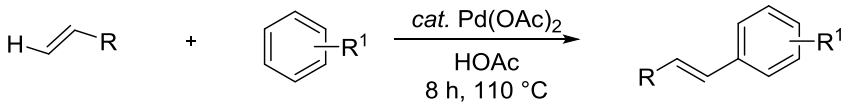
The first synthesis of economically relevant styrene derivatives, which are key structural motifs in natural products, *via* transition metal-catalyzed oxidative alkenylation was published in 1967 by *Fujiwara* and *Moritani*.[43] The reaction was first conducted with a palladium-styrene-complex, which reacted with the arene, yielding the stilbene (Scheme 1.19 a). Immediately after this the amount of the palladium complex could be reduced to catalytic amounts (Scheme 1.19 b).

a)



45 **4b** **46** **47**

b)



17 **4b** **46a**

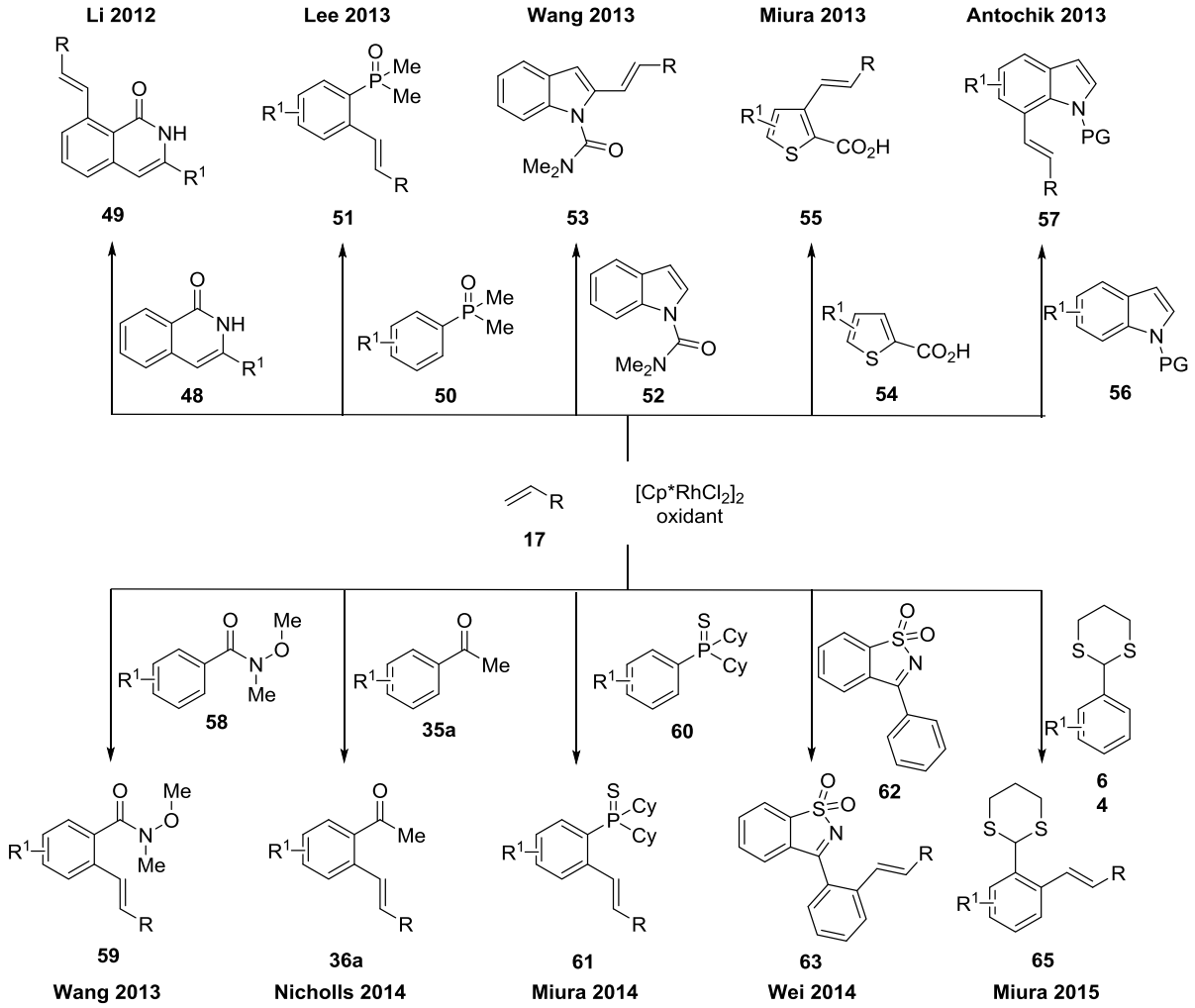
Scheme 1.19: *Fujiwara-Moritani*-Reaction.

Thereupon, various applications of palladium catalysts with different oxidants and additives on different substrates were systematically studied.[44]

The search of efficient transition metal-catalysts for C−C bond formation led to rhodium catalysis. In recent years various efficient and selective, yet relatively expensive rhodium catalysts were used for the oxidative alkenylation (Scheme 1.20).[45]

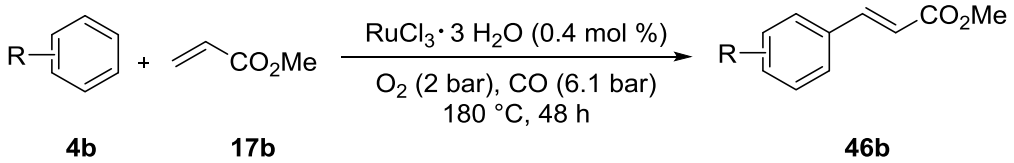
[43] (a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *12*, 1119–1122; (b) Y. Fujiwara, I. Moritani, M. Matsuda,*Tetrahedron* **1968**, *24*, 4819-4824.

[44] (a) S. R. Kandukuri, J. A. Schiffner, M. Oestreich, *Angew. Chem. Int. Ed.* **2012**, *51*, 1265–1269; (b) Y.-H. Xu, J. K. Cheng, M. T. Low, T.-P. Loh, *Angew. Chem. Int. Ed.* **2012**, *51*, 5701–5705; (c) C. Wang, H. Ge, *Chem.–Eur. J.* **2011**, *17*, 14371–14374; (d) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228; (e) D.-H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, **2010**, *327*, 315–319; (f) M. Miyasaka, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2010**, *75*, 5421–5424; (g) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460–461; (h) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc*. **2009**, *131*, 5072–5074; (i) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett*. **2008**, *10*, 1159–1162; (j) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem. Int. Ed*. **2005**, *44*, 3125–3129; (k) M. Dams, D. E. De Vos, S. Celen and P. A. Jacobs, *Angew. Chem. Int. Ed.* **2003**, *42,* 3512–3515; (l) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124,* 1586–1587; (m) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, *J. Org. Chem*. **1998**, *63*, 5211–5215.



Scheme 1.20: Selected examples of rhodium-catalyzed alkenylations.

The use of cheaper ruthenium-catalysts was reported by *Milstein* in 2001 (Scheme 1.21).[46]



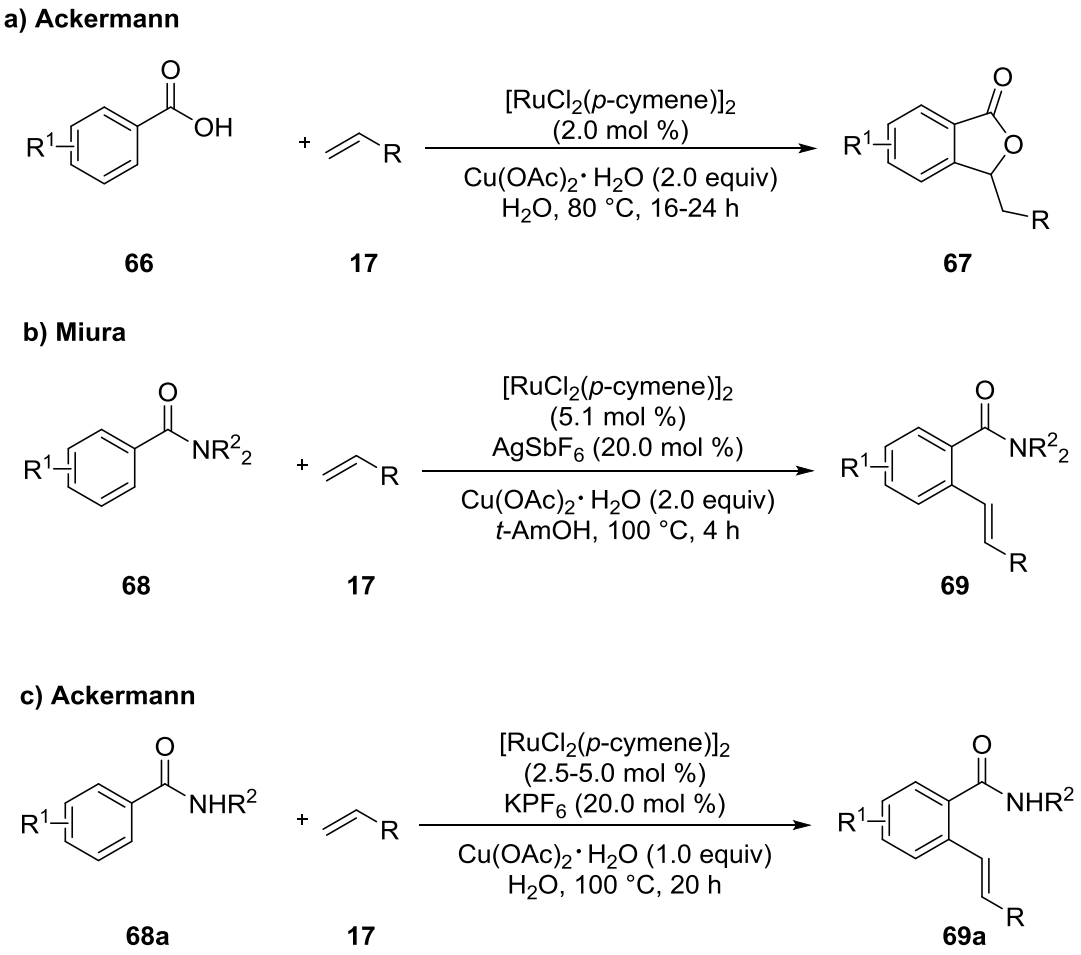
Scheme 1.21: Oxidative alkenylation of arenes by *Milstein*.

The scope of this reaction was limited to simple arenes and methyl acrylate as alkene. Notably, the reaction worked without directing group and with oxygen as the terminal oxidant, albeit under high pressure and harsh reaction conditions. The ruthenium-catalyzed reaction

[45] (a) J. Mo, S. Lim, S. Park, T. Ryu, S. Kim, P. H. Lee, *RSC Adv*. **2013**, *3*, 18296–18299; (b) Y. Yokoyama, Y. Unoh, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2014**, *79*, 7649−7655; (c) T. Iitsuka, P. Schaal, K Hirano, T. Satoh, C. Bolm, M. Miura, *J. Org. Chem*. **2013**, *78*, 7216−7222; (d) S. Kathiravan, I. A. Nicholls, *Eur. J. Org. Chem.* **2014**, 7211–7219; (e) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *Chem. Eur. J*. **2013**, *19*, 11863–11868; (f) Z. Song, R. Samanta, A. P. Antonchick, *Org. Lett.* **2013**, *15*, 5662−5665. (g) N.-J. Wang, S.-T. Mei, L. Shuai, Y. Yuan, Y. Wie, *Org. Lett.* **2014**, *16*, 3040−3043; (h) P. Zhao, R. Niu, F. Wang, K. Han, X. Li, *Org. Lett.* **2012**, *14*, 4166−4169; (i) Y. Unoh, K. Hirano, T. Satoh, M. Miura, *Org. Lett*. **2015**, *17*, 704−707; (j) Y. Wang, C. Li, Y. Li, F. Yin, X.-S. Wanga, *Adv. Synth. Catal.* **2013**, *355*, 1724–1728.

[46] H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337–338.

was continuously extended by *Ackermann*, *Miura* and *Satoh*.[47] Selected examples from *Miura* and *Ackermann* are represented in Scheme 1.22, including the use of the air-stable catalyst $[RuCl_2(p\text{-cymene})]_2$, copper(II) acetate as the oxidant and an additive.

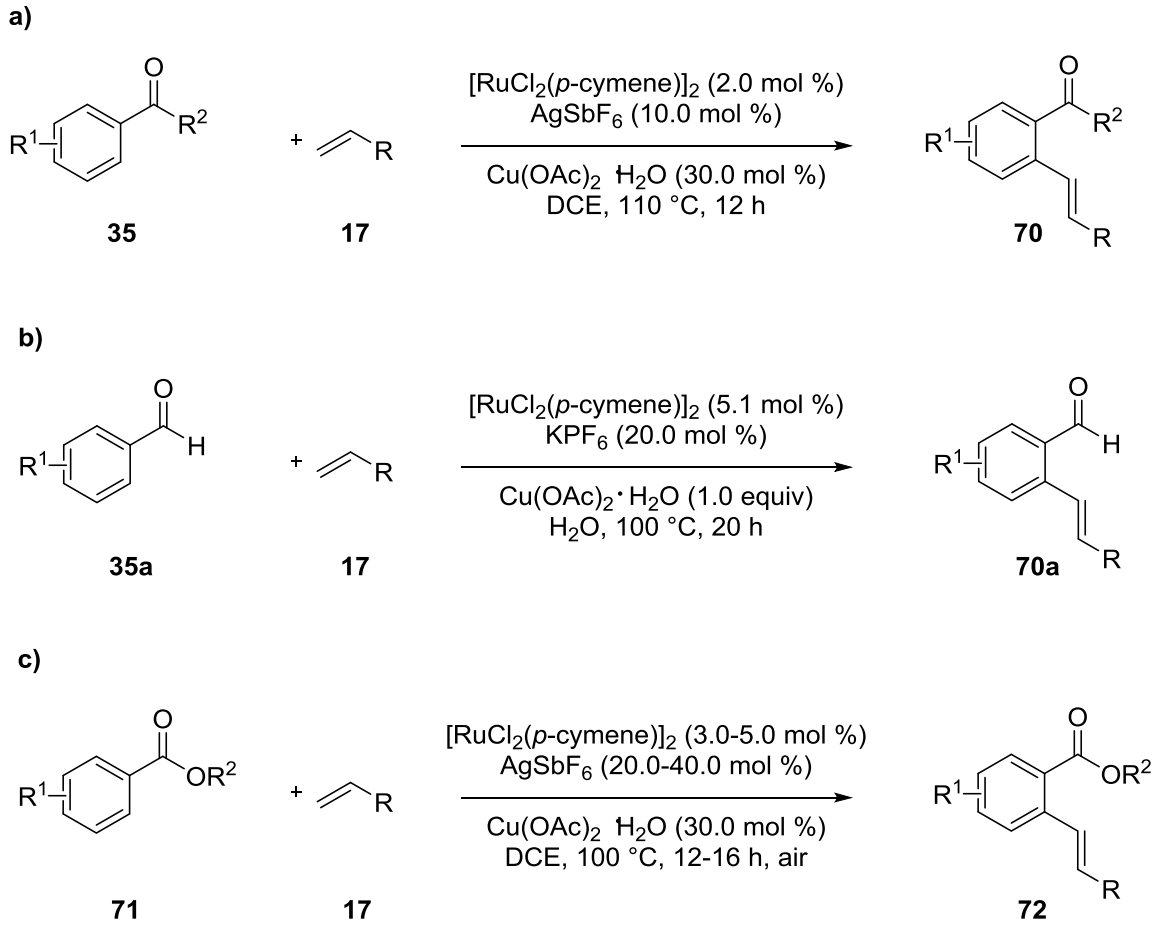


Scheme 1.22: Ruthenium(II)-catalyzed oxidative alkenylation of benzamides.

Further improvements in the ruthenium(II)-catalyzed reactions were achieved because of the combination of reduced amounts of copper acetate monohydrate and an aerobic atmosphere (Scheme 1.23 a).[48] Particularly notable, is the functionalization of benzaldehydes (Scheme 1.23 b).

[47] (a) Y. Hashimoto, T. Ortloff, K. Hirano, T. Satoh, C. Bolm, M. Miura, *Chem. Lett.* **2012**, *41*, 151–153; (b) L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, *Org. Lett.* **2012**, *14*, 728–731; L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153-4155.

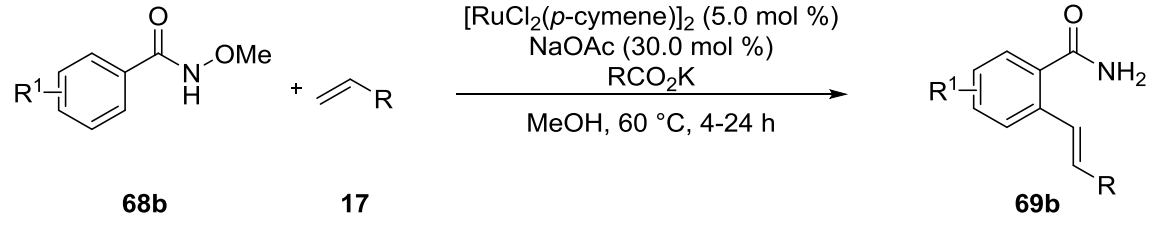
[48] (a) K. Graczyk, W. Ma, L. Ackermann, *Org. Lett.* **2012**, *14*, 4110–4113; (b) K. Padala, S. Pimparkar, P. Madasamy, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 7140–7142; (c) K. Padala, M. Jeganmohan, *Org. Lett.* **2011**, *13*, 6144–6147; (d) K. Padala, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 1134–1137.



Scheme 1.23: Ruthenium(II)-catalyzed oxidative alkenylation of arenes under air.

Meanwhile, the standard reaction conditions using copper acetate as the oxidant is indeed convenient, however, heavy metal waste is still produced as by-product.

An elegant way of ruthenium-catalyzed reactions avoiding this waste is the use of prefunctionalized starting materials, bearing a directing group containing an internal oxidant (Scheme 1.24).[49]

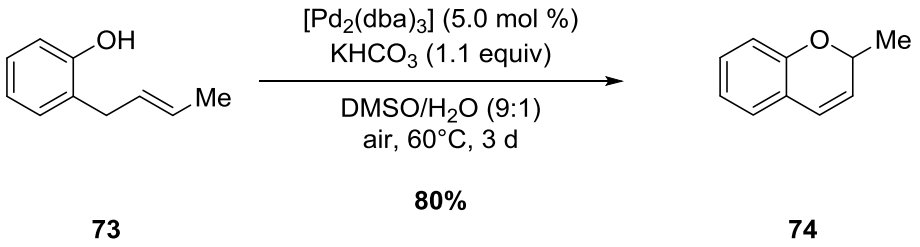


Scheme 1.24: Ruthenium-catalyzed oxidative alkenylation with internal oxidants.

The most abundant and inexpensive oxidant that can be used in oxidative C−H bond functionalization is air. So far, there are only few examples of C−H bond functionalization using air as the sole oxidant (Scheme 1.25). The palladium-catalyzed synthesis of chromene

[49] (a) F. Yang, L. Ackermann. *J. Org. Chem.* **2014**, *79*, 12070−12082; (b) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548−6551.

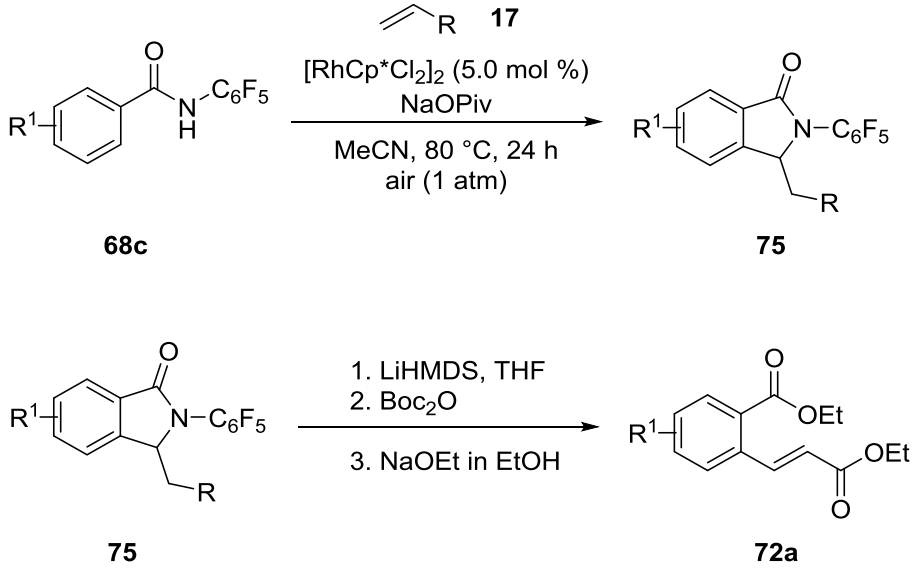
structures by 6-endo cyclization of *ortho*-allylic phenols with excellent yields was reported by *Larock* in 1998.[50] Ideally, the reaction was accomplished with air as the oxidant. Unfortunately, full conversion of this reaction was obtained only after three days.



73 **74**

Scheme 1.25: 6-endo Cyclization of *ortho*-allylic phenols with air as sole oxidant.

Recently, the first rhodium-catalyzed example using air as sole oxidant was published by *Yu* in 2015 (Scheme 1.26).[51] There, *N*-perfluoroaryl benzamides **68c** led to the *ortho*-alkenylation. The *γ*–lactam products are readily converted to the olefinated products, by treating the lactam with LiHMDS, Boc_2O and sodium ethanolate.



68c **75**

75 **72a**

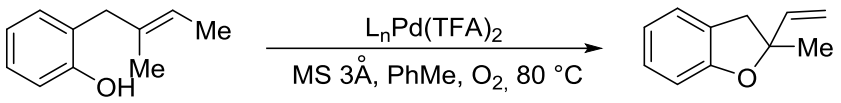
Scheme 1.26: Rhodium-catalyzed direct alkenylation with air as terminal oxidant.

Despite this progress, applying these economic conditions remained an extremely challenging task. In contrary, the use of ambient oxygen in transition metal-catalyzed C−H bond functionalization gained more attention in recent years. In 1999, *Uemura* published the palladium-catalyzed oxidative ring cleavage of *tert*-cyclobutanols under an oxygen

[50] (a) R. C. Larock, T. R. Hightower, L. A. Haswold, K. P- Peterson, *J. Org. Chem.* **1996**, *61*, 3584−3585; (b) R. C. Larock, L. Wei, T. R. Hightower, *Synlett*, **1998**, *5*, 522−524.

[51] Y. Lu, H.-W. Wang, J. E. Spangler, K. Chen, P.-P. Cui, Y. Zhao, W.-Y. Sun, J.-Q. Yu, *Chem. Sci.* **2015**, *6*, 1923−1927.

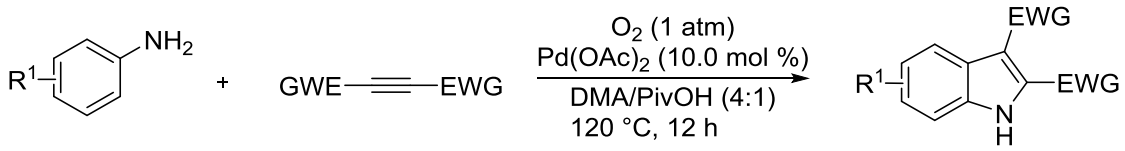
atmosphere.[52] Based on this publication *Stoltz* developed the first palladium-catalyzed cyclization of heteroatoms onto pedant olefins in 2005 (Scheme 1.27).[53]



76 **77**

Scheme 1.27: Palladium-catalyzed cyclization with O_2 as the oxidant.

In 2009, *Jiao* succeeded in the synthesis of indoles from simple anilines and alkynes (Scheme 1.28).[54] The palladium catalyst used ambient oxyen and was limited to alkynes with electron withdrawing substituents.



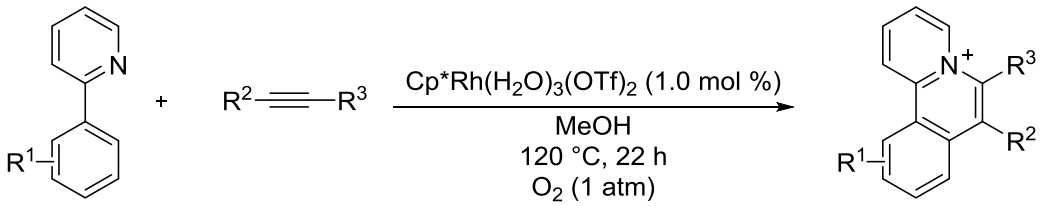
78 CO_2Me = **79** **80**

Scheme 1.28: Palladium-catalyzed oxidative alkyne annulation with oxygen.

Subsequently, several groups reported on the palladium-catalyzed oxidative C−H bond functionalization with oxygen.[55]

In spite of this progress in palladium-catalyzed oxidative reactions with oxygen as the terminal oxidant, the use of other metals remained difficult. The first rhodium-catalyzed reaction using molecular oxygen was reported by *Huang* in 2013, exploring a rhodium catalyst in the oxidative alkyne annulation of phenylpyridines (Scheme 1.29).[56] In 2014, *Huang* could expand this system for the synthesis of alkenylated indole derivatives.[57]

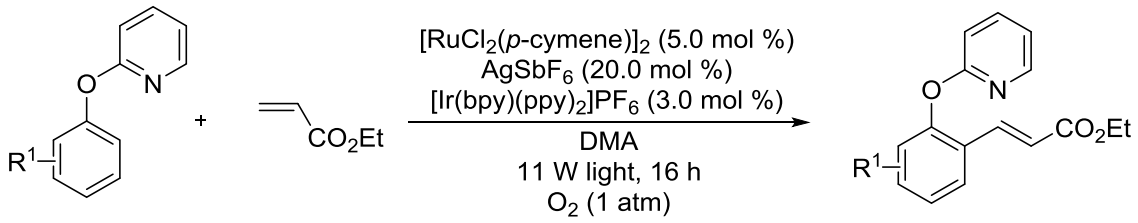
[52] T. Nishimura, K. Ohe, S. Uemura, *J. Am. Chem. Soc*. **1999**, *121*, 2645−2646.
[53] R. M. Trend, Y. K. Ramtohul, B. M. Stoltz, *J. Am. Soc.* **2005**, *127*, 17778−17788.
[54] Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 4572−4576.
[55] (a) Y. Dong, S. Mao, Y.-R. Gao, D.-D. Guo, S.-H. Guo, B. Li, Y.-Q. Wang, *RSC Adv.* **2015**, *5*, 23727–23736; (b) Z.-L. Yan, W.-L. Chen, Y.-R. Gao, S. Mao, Y.-L. Zhang, Y.-Q. Wanga, *Adv. Synth. Catal.* **2014**, *356*, 1085–1092; (c) G. Zhang, H. Yu, G. Qin, H. Huang, *Chem. Commun.* **2014**, *50*, 4331−4334; (d) P. Gandeepan, C.-H. Cheng, *J. Am. Chem. Soc.* **2012**, *134*, 5738−5741; (e) Y.-H. Xu, Y. K. Chok, T.-P. Loh, *Chem. Sci*. **2011**, *2*, 1822–1825.
[56] G. Zhang, L. Yang, Y. Wang, Y. Xie, H. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 8850−8853.
[57] L. Yang, G. Zhang, H. Huang, *Adv. Synth. Catal.* **2014**, *356*, 1509–1515.



19 **81** **82**

Scheme 1.29: Rhodium-catalyzed oxidative alkyne annulation with oxygen as the oxidant.

The first ruthenium-catalyzed oxidative C−H bond functionalization with molecular oxygen was published in 2015 by *Rueping*.[58] The group of *Rueping* used a combination of $[RuCl_2(p\text{-cymene})]_2$ and an expensive iridium photoredox-catalyst with oxygen as oxidant and silver hexaflouroantimonate as additive (Scheme 1.30).

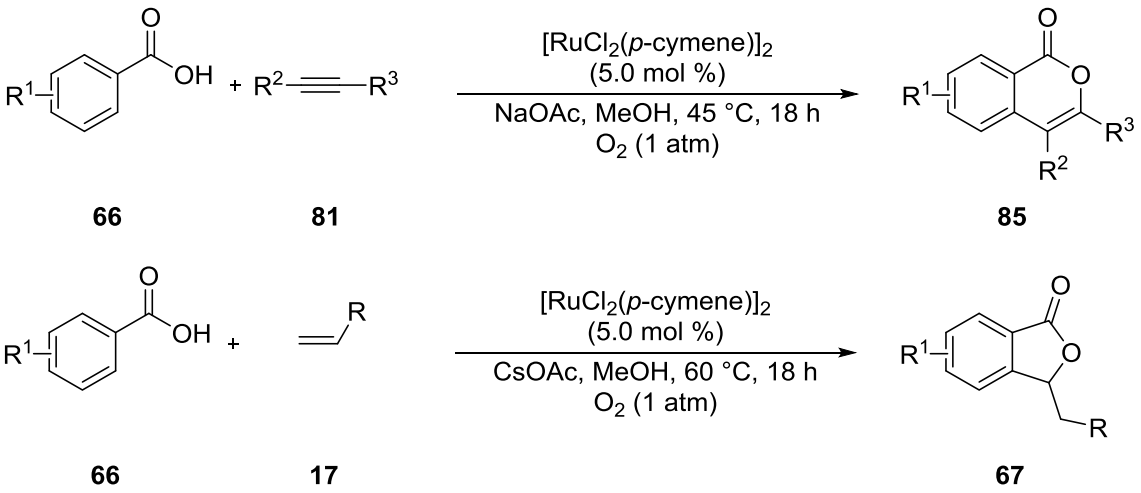


83 **17c** **84**

Scheme 1.30: Ruthenium-photoredox-catalyzed oxidative alkenylation of phenoxypyridines with oxygen.

Shortly after *Rueping´*s report, *Ackermann* published the ruthenium-catalyzed C−H activation/alkyne annulation with oxygen as the sole oxidant (Scheme 1.31).[59] The mild reaction conditions with sodium acetate as carboxylate ligand in methanol at 45 °C represents a special key feature in the advancement of ruthenium(II)-catalyzed aerobic functionalization and in the synthesis of heterocyclic compounds, such as isocoumarins or phthalides.

[58] D. C. Fabry, M. A. Ronge, J. Zoller, M. Rueping, *Angew. Chem. Int. Ed*. **2015**, *54*, 2801–2805.
[59] S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 5513–5517.



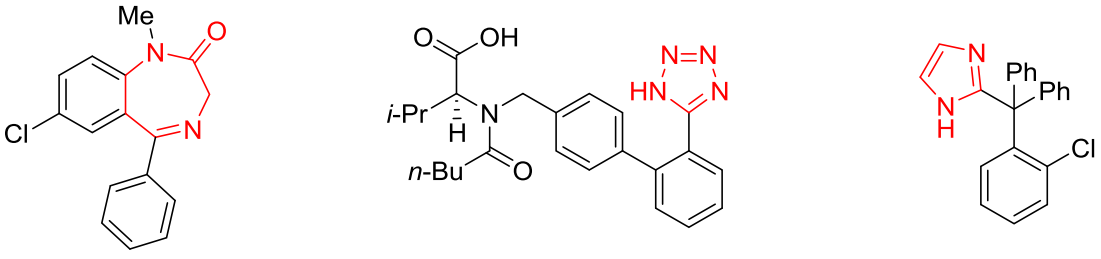
66 **81** **85**

66 **17** **67**

Scheme 1.31: Ruthenium-catalyzed oxidative annulations of carboxylic acids with oxygen as oxidant.

1.5 C−H Bond Functionalization for the Efficient Synthesis of Heterocyclic Compounds

Heterocyclic compounds are important key structural motifs in pharmaceutical and medicinal products.[60] Scheme 1.32 presents some selected substances with heterocyclic moieties. The heterocyclic core is highlighted with red colour. The core of the diazepam is a diazepinone structure.[61] Valsartan, which is used for hypertension medication, is produced up to 1000 tonnes per year.[62] The heterocycle contained in this molecule is a tetrazole. The last key structural motif in this Scheme is an imidazole containing antibiotikum.[63]



Diazepam **Valsartan** **Clotrimazol**

Scheme 1.32: Examples of heterocyclic containing pharmaceuticals.

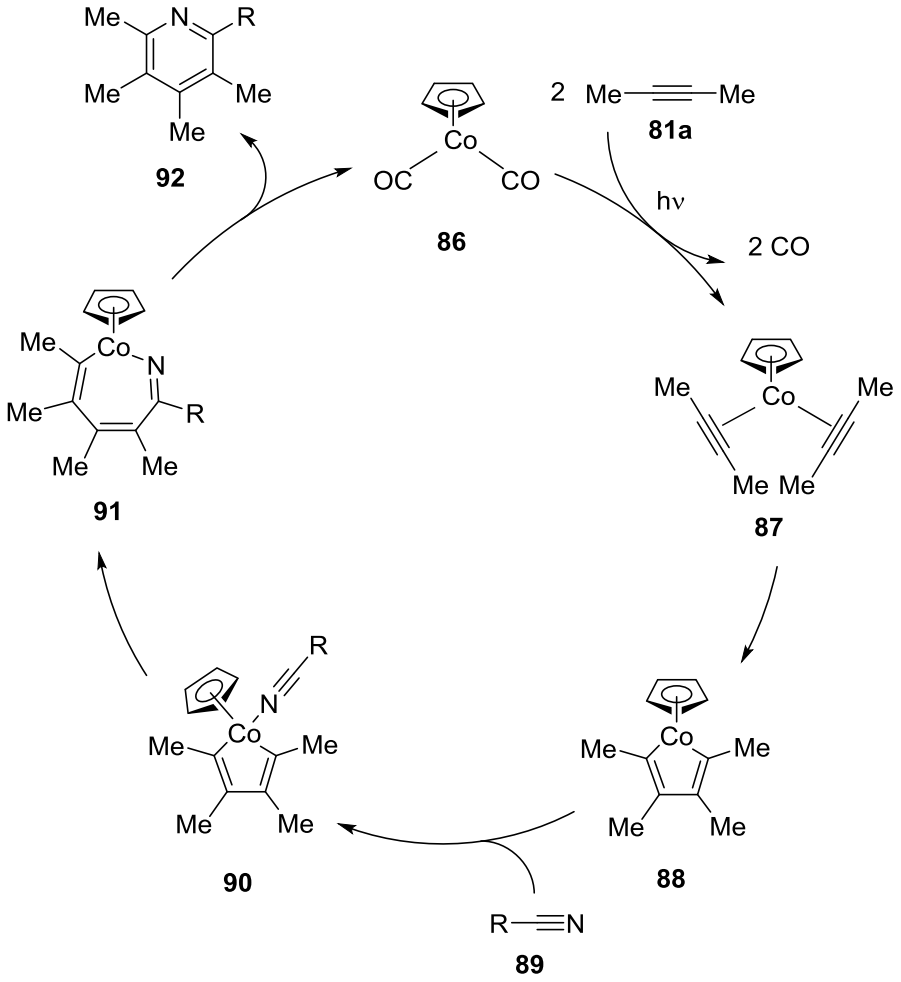
[60] Selected Reviews: a) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A. M. Almerico, *Eur. J. Org. Chem.* **2014**, *16*, 3289–3306; b) D. Gonzaga, G. Tadeu, D. R. da Rocha, F. de C. da Silva, V. F. Ferreira, *Med. Chem.* **2013**, *13*, 2850–2865; c) M. Juricek, P. H. Kouwer, A. E. Rowan, *Chem. Comm.* **2011**, *47*, 8740–8749; d) S. G. Agalve, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696–2718; e) C. O. Kappe, E. Van der Eycken, *Chem. Soc. Rev.* **2010**, *39*, 1280–1290; f) K. D. Hänn, D. A. Leigh, *Chem. Soc. Rev.* **2010**, *39*, 1240–1251; g) A. H. El-Sagheer, T. Brown, *Chem. Soc. Rev.* **2010**, *39*, 1388–1405; h) A. Qin, J. W. Y. Lam, B. Z. Tang, *Chem. Soc. Rev.* **2010**, ***39***, 2522–2544.

[61] Martin Wehling, *Klinische Pharmakologie.* 1. Aufl., Georg Thieme Verlag, Stuttgart, **2005**, S. 487.

[62] (a) N. B. Mistry, A. S. Westheim, S. E. Kjeldsen, *Expert Opin. Pharmacother.* **2006**, *7*, 575–581; (b) S. E. Kjeldsen, H. R. Brunner, G. T. McInnes, P. Stolt, *Aging Health,* **2005**, *1*, 27–36.

[63] (a) M. Plempel, K. Bartmann, K. H. Büchel, E. Regel, *Deutsche Medizinische Wochenschrift*, **1969**, *94*, 1356–1367; (b) K. H. Büchel, W. Draber, E. Regel, M. Plempel, *Arzneimittel-Forschung / Drug Research*, **1972**, *22*, 1260–1272.

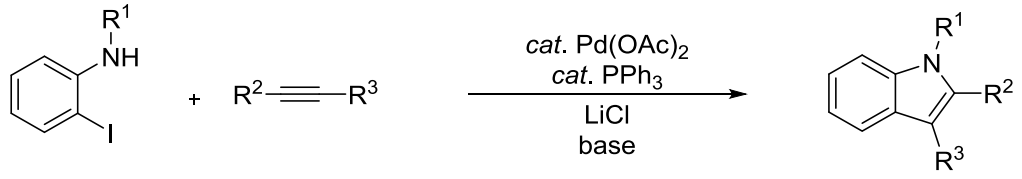
Because of the widespread use of heterocycles, there is a continued strong desire to synthesize these molecules in an economic way. The transition metal-catalyzed synthesis of heterocycles by alkyne annulation is of major significance. Especially cobalt-catalyzed annulations play an important role in heterocyclic chemistry, for example the *Pauson-Khand* reaction,[64] the *Bönnemann*-pyridine synthesis[65] and the *Vollhardt*-pyridine-synthesis,[66] which is shown in Scheme 1.33, including the reaction mechanism.



Scheme 1.33: Cobalt-catalyzed *Vollhardt*-pyridine-synthesis.

An important example of the palladium-catalyzed cross-coupling reaction is the *Larock*-synthesis of indoles (Scheme 1.34).[67] In this reaction *ortho*-iodoanilinine reacts with an alkyne to give the indole.

[64] I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, Chem. Comm. **1971**, 1, 36
[65] H. Bönnemann, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 505–515.
[66] (a) K. P. Vollhardt, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–556; (b) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085−1094.
[67] (a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6690–6692; (b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662.

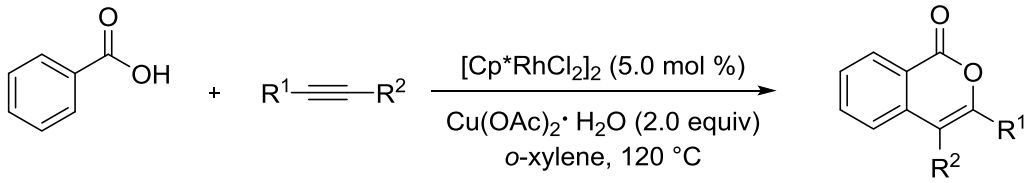


93 **81** **80a**

Scheme 1.34: *Larock*-synthesis of indole.

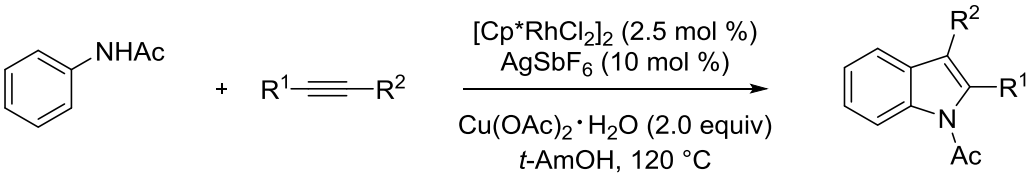
The access to heterocyclic core structures *via* transition metal-catalyzed alkyne annulation is a very important aim and was extensively investigated by *Ackermann*, *Fagnou*, *Miura* and others.[68, 69] Selected examples of rhodium-catalyzed alkyne annulations are presented in Scheme 1.35.[55, 70]

a)



66 **81** **85**

b)



94 **81** **80b**

Scheme 1.35: Rhodium-catalyzed alkyne annulation.

However, the ruthenium-catalyzed alkyne annulation was also achieved with various substrates and economical catalyst. Selected examples for ruthenium-catalyzed alkyne annulations are shown in Scheme 1.36. The ruthenium-catalyzed annulation of alkynes with benzamides leading to pyridinones is shown in Scheme 1.36 a.[68b] Interestingly, *Ackermann*

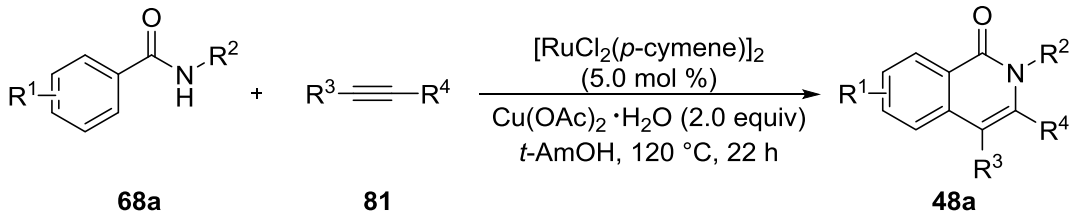
[68] (a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651–3678; (b) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382; (c) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212–11222; (d) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744–746; (e) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339; (f) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051.

[69] (g) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475.

[70] K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5367.

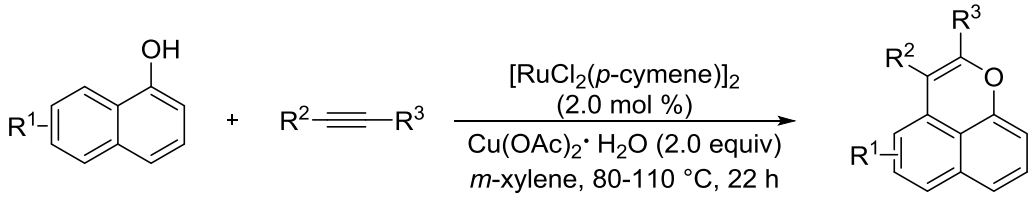
and co-workers managed to find appropriate reaction conditions for the successful alkyne annulation with naphtholes and 2-phenylpyrazoles (Scheme 1.36 b and c).[71]

a) Ruthenium(II)-catalyzed annulation of alkynes by benzamides.



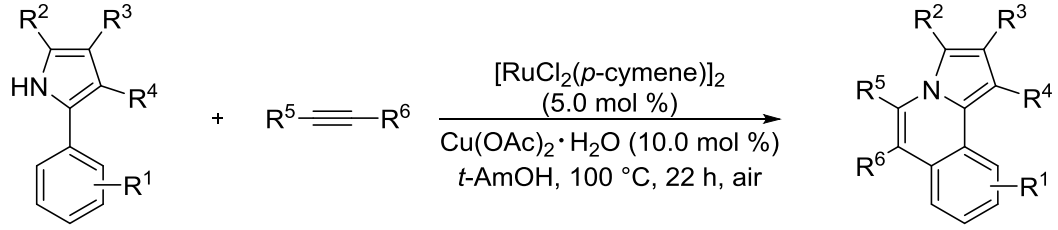
68a **81** **48a**

b) Ruthenium(II)-catalyzed annulation of alkynes by naphthols.



95 **81** **96**

c) Ruthenium(II)-catalyzed annulation of alkynes by arene pyrazoles.



97 **81** **98**

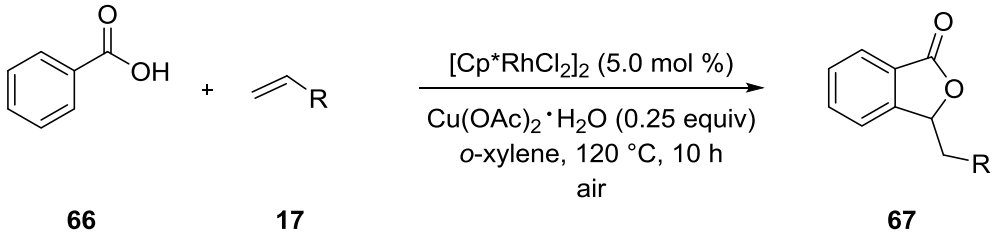
Scheme 1.36: Ruthenium(II)-catalyzed annulation of alkynes.

The transition metal-catalyzed synthesis of heterocycles by alkyne annulation is an important research area.

A second important field is the annulation with alkenes. In contrast to the alkyne annulation, the cyclization is due to an oxa- or aza-*Michael* reaction.

An early example was reported by *Miura* on the alkene annulation of benzoic and acrylic acids with acrylates (Scheme 1.37).[72] A stoichiometric amount of copper acetate was not necessary.

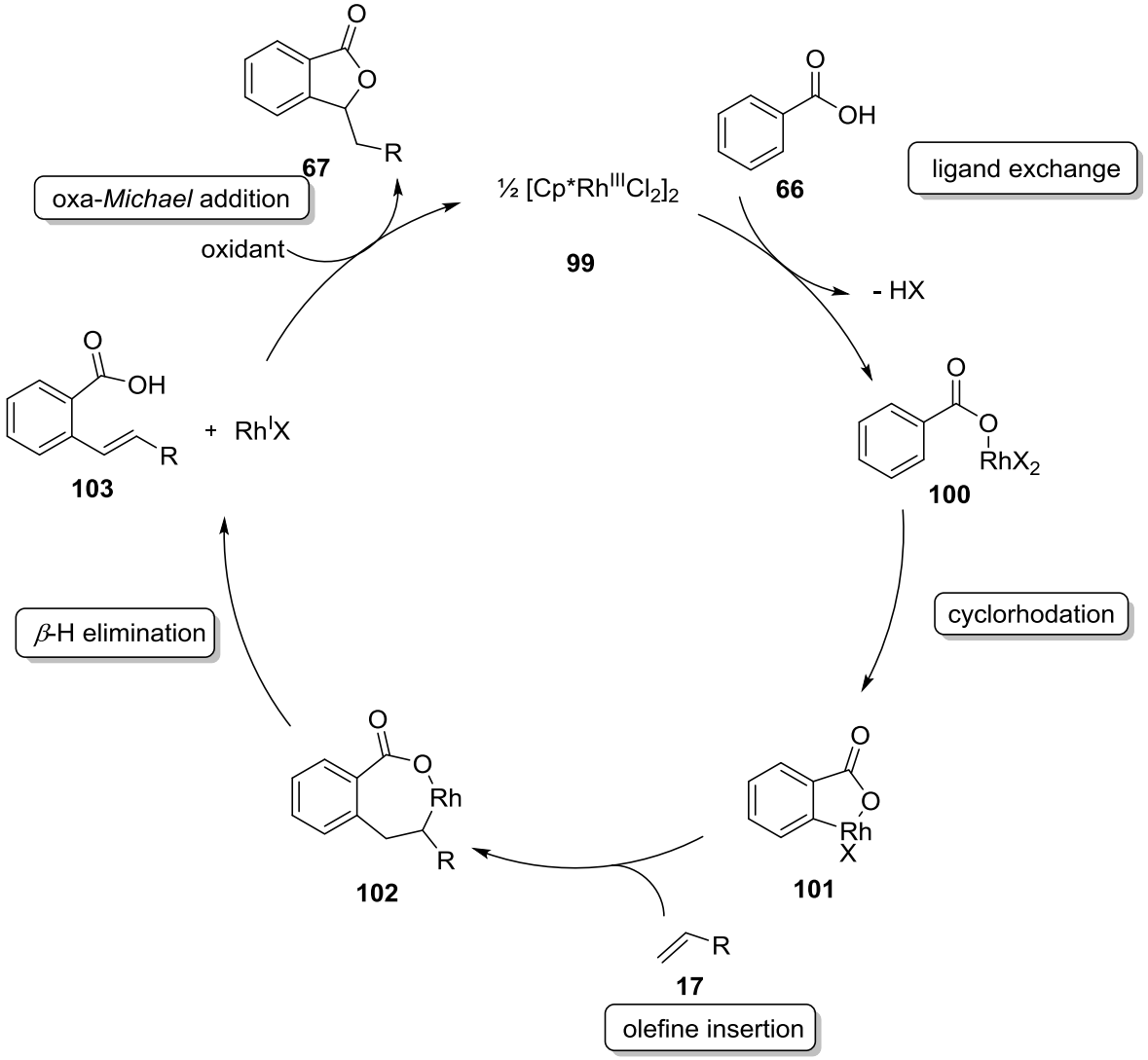
[71] (a) L. Ackermann, L. Wang, A. V. Lygin, *Chem. Sci.* **2012**, *3*, 177–180; (b) V. S. Thirunavukkarasu, M. Donati, L. Ackermann, *Org. Lett.* **2012**, *14*, 3416–3419.



66 **17** **67**

Scheme 1.37: Rhodium-catalyzed annulation of alkynes with benzoic acids **66**.

The proposed mechanism of this transformation is shown in Scheme 1.38.[73] In the first step the benzoic acid coordinates to the rhodium-catalyst to give **100**. Thereafter, the cyclorhodation takes place and affords the rhodacycle **101**. Subsequent alkene insertion occurs to produce the corresponding seven-membered rhodacycle **102**, which undergoes *β*-hydride elimination. Afterwards, the nucleophilic cyclization results in **67**. Reoxidation in the presence of copper(II) acetate regenerates the catalytic species.

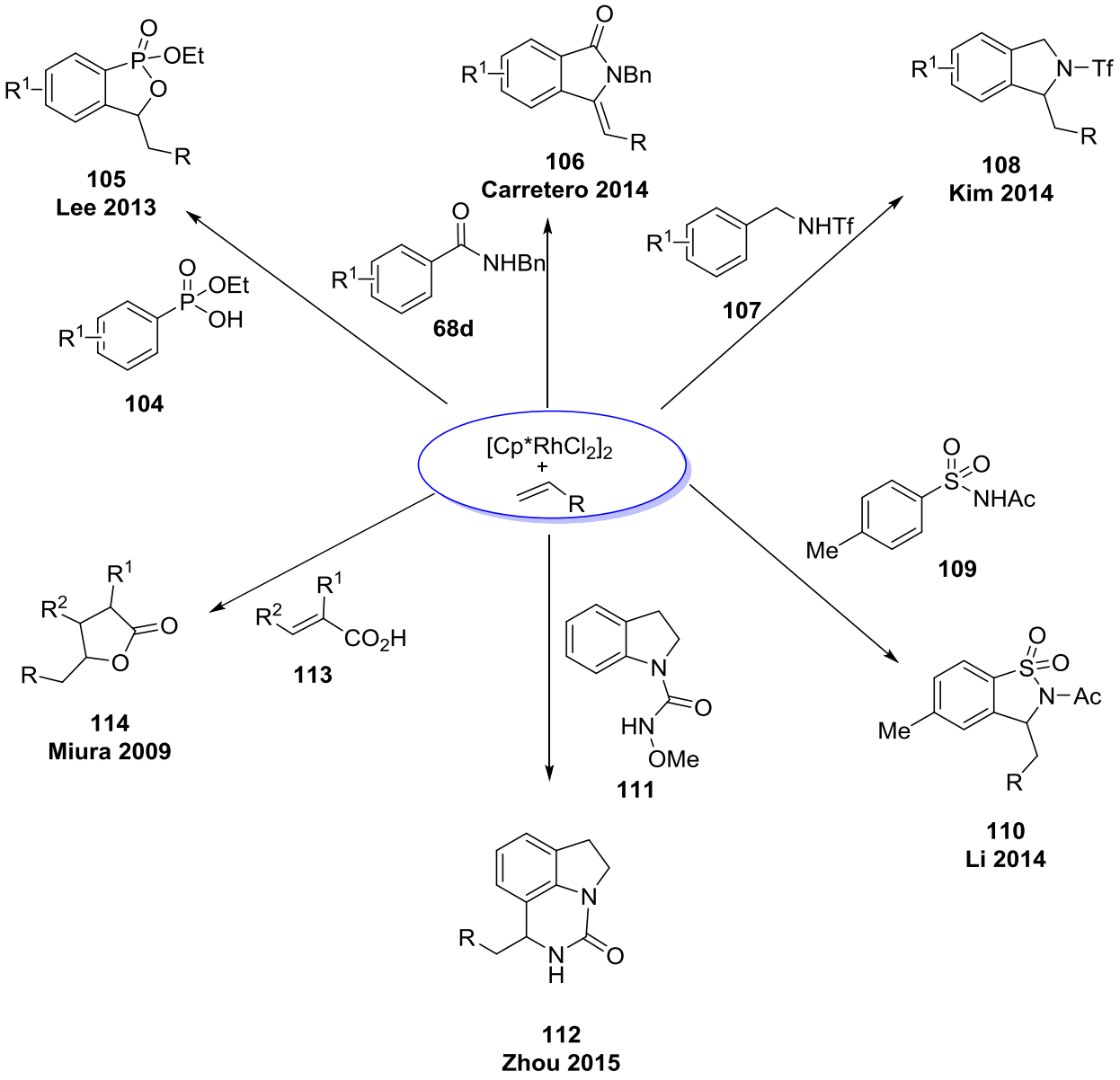


Scheme 1.38: Mechanism of rhodium-catalyzed synthesis of phthalides **67**.

[72] K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407−1409.
[73] S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6295−6298.

In 2013, *Lee* published the rhodium-catalyzed synthesis of benzoxaphosphol oxides.[74] Subsequently, various other rhodium-catalyzed reactions were developed.[62, 75]

Several rhodium-catalyzed alkene cyclization reactions were published in recent years (Scheme 1.39).[68b, 68d-f, 73, 76] In Scheme 1.39 the versatility of this reaction is presented.



Scheme 1.39: Rhodium-catalyzed C−H olefination followed by oxa- and aza-*Michael*-reactions.

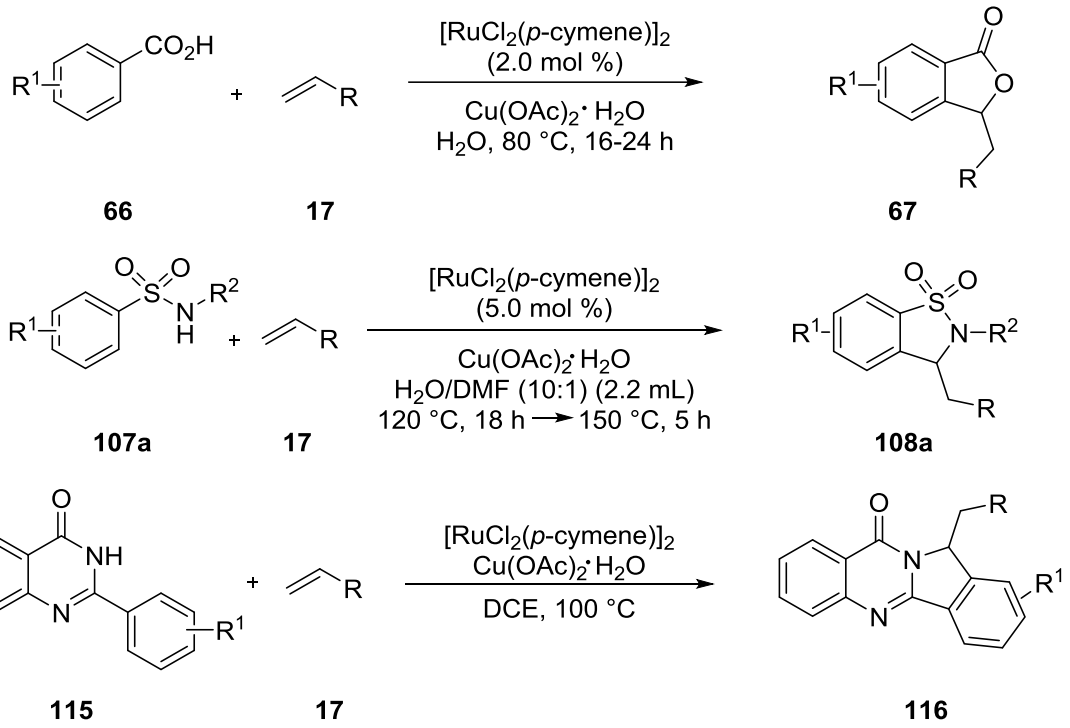
In 2011, *Ackermann* and co-workers succeeded in the first ruthenium-catalyzed C−H olefination followed by oxa-*Michael* reaction using benzoic acids for the synthesis of

[74] T. Ryu, J. Kim, Y. Park, S. Kim, P. H. Lee, *Org. Lett.* **2013**, *15*, 3986–3989.

[75] Selected examples: (a) X. Wang, H. Tang, H. Feng, Y. Li, Y. Yang, B. Zhou, *J. Org. Chem.* **2015**, *80*, 6238−6249; (b) S. Han, Y. Shin, S. Sharma, N. K. Mishra, J. Park, M. Kim, M. Kim, J. Jang, I. S. Kim, *Org. Lett.* **2014**, *16*, 2494−2497; (c) N. K. Mishra, J. Park, S. Sharma, S. Han, M. Kim, Y. Shin, J. Jang, J. H. Kwak, Y. H. Jung, I. S. Kim, *Chem. Commun.* **2014**, *50*, 2350−2352; (d) A. M. Martínez, N. Rodríguez, R. G. Arrayás, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 6105−6107; (d) W. Xie, J. Yang, B. Wang, B. Li, *J. Org. Chem.* **2014**, *79*, 8278−8287.

[76] (a) T. Ryu, J. Kim, Y. Park, S. Kim, P. H. Lee, *Org. Lett.* **2013**, *15*, 3986–3989

phthalides.[77] Further studies by *Ackermann* resulted in sultams.[78] Studies by *Xuang* resulted in the synthesis of quinazolinones (Scheme 1.40).[79]

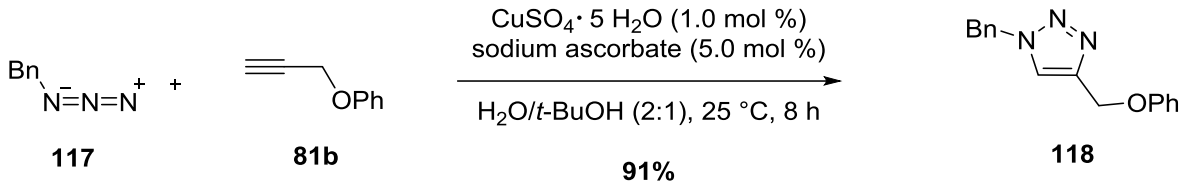


Scheme 1.40: Ruthenium-catalyzed C−H olefination followed by oxa- and aza-*Michael*-reactions.

1.6 Triazole Syntheses and Functionalizations

Triazoles are of great importance because of their biological and pharmaceutical properties. The core structure of 1,2,3-triazoles can be synthesized by two main ways. In general, 1,2,3-triazoles are synthesized by the thermal 1,3-dipolar cycloadditions of alkynes and azides leading to 1,4-disubstituted 1,2,3-triazoles. This reaction was pioneered by *Rolf Huisgen* in 1963.[80] A major problem of this reaction was the separation of the different regioisomeric products. This problem was solved by *Meldal*, using copper(I) catalysts.[81] A robust and useful reaction procedure was developed by *Sharpless* and *Fokin* (Scheme 1.41).[82]

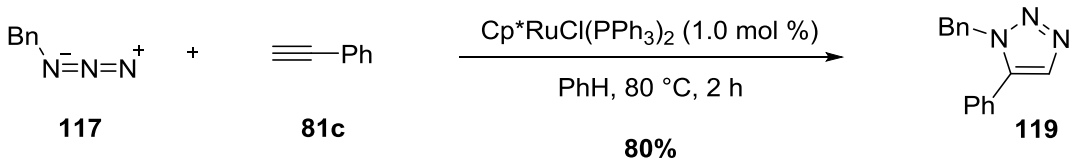
[77] L. Ackermann, J. Pospech, *Org. Lett.* **2011**, 13, 4153–4155.
[78] W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248−15251.
[79] Y. Zheng, W.-B. Song, S.-W. Zhang, L.-J. Xuan, *Org. Biomol. Chem.* **2015**, *13*, 6474–6478.
[80] R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565−598.
[81] C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057−3064.
[82] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596−2599.



117 **81b** **91%** **118**

Scheme 1.41: Copper-catalyzed [3+2]-cycloaddition for the synthesis of 1,2,3-triazoles.

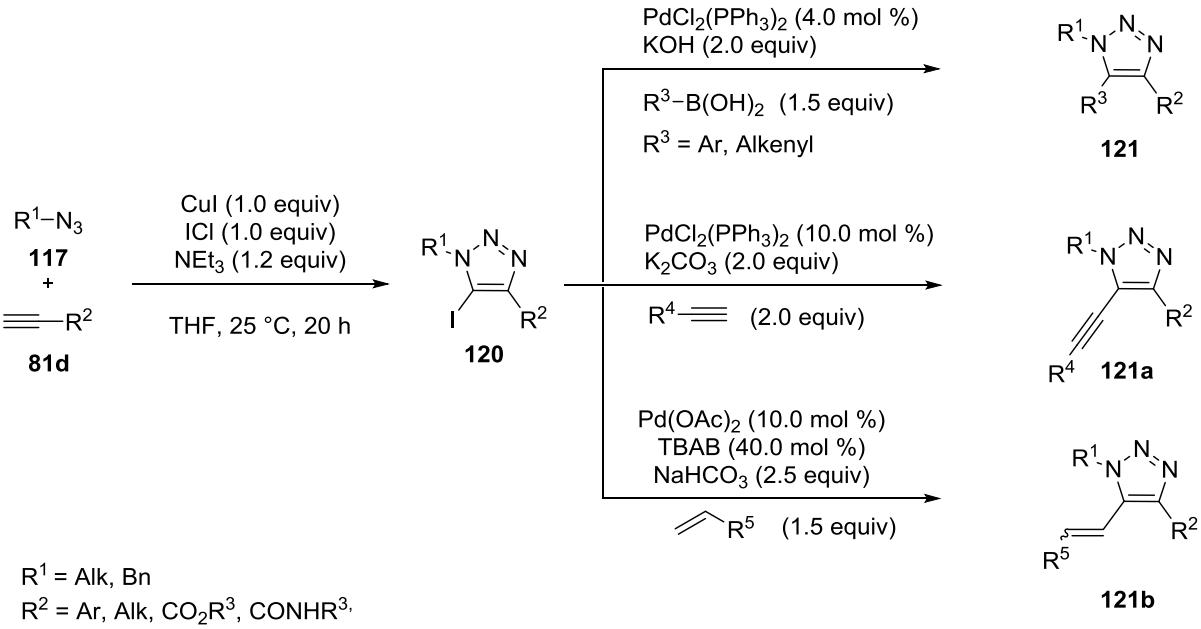
The complementary selectivity can be achieved by using ruthenium instead of copper catalysts, giving 1,5-disubstituted triazoles (Scheme 1.42).



117 **81c** **80%** **119**

Scheme 1.42: Ruthenium-catalyzed [3+2]-cycloaddition for the synthesis of 1,2,3-triazoles.

While 1,4-disubstituted triazoles can be obtained by using catalytic amounts of copper(II) acetate, the use of stoichiometric amounts of copper salts led to fully substituted 1,2,3-triazoles (Scheme 1.43).[83]

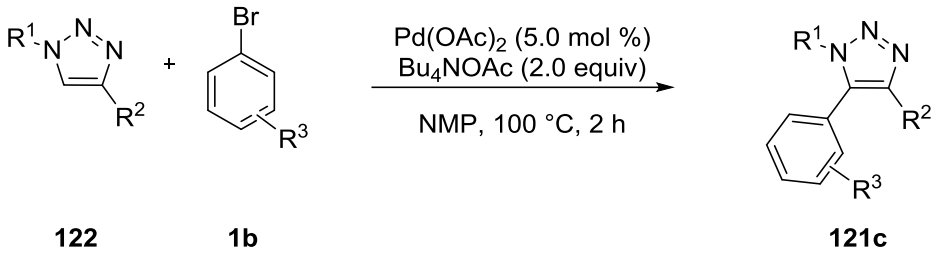


Scheme 1.43: Copper-catalyzed synthesis of fully substituted 1,2,3-triazoles.

Fully substituted 1,2,3-triazoles can also be prepared by functionalization of the 1,4-disubstituted triazoles, with bromoalkanes and palladium complexes as catalyst (Scheme

[83] Y.-M. Wu, J. Deng, Y. Li and Q.-Y. Chen, *Synthesis* **2005**, 1314−1318.

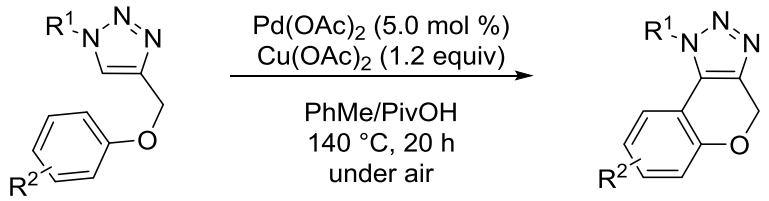
1.44).[84] Several arylation reactions were studied with different arylating reagents, such as chlorides or tosylates.[85]



122 **1b** **121c**

Scheme 1.44: Palladium-catalyzed arylation of 1,4 disubstituted 1,2,3-triazoles.

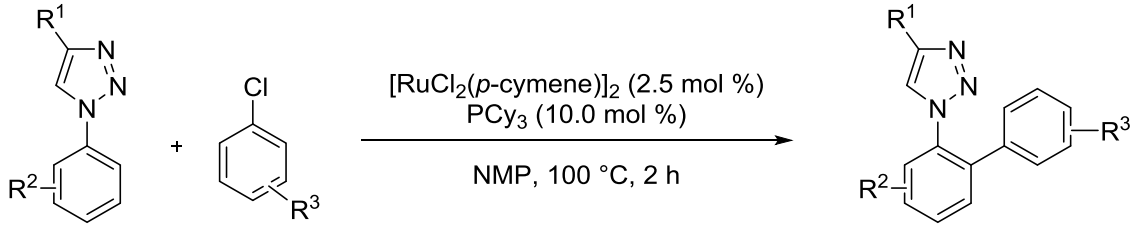
Functionalization of 1,4-substituted triazoles through twofold C−H activation could be obtained in an intramolecular fashion (Scheme 1.45).[86]



122a **120d**

Scheme 1.45: Palladium-catalyzed intramolecular arylation of 1,4-disubstituted 1,2,3-triazoles.

Also the use of the triazole moiety as a directing group led to several functionalized substrates. One representative example is shown in Scheme 1.46.[85, 87]



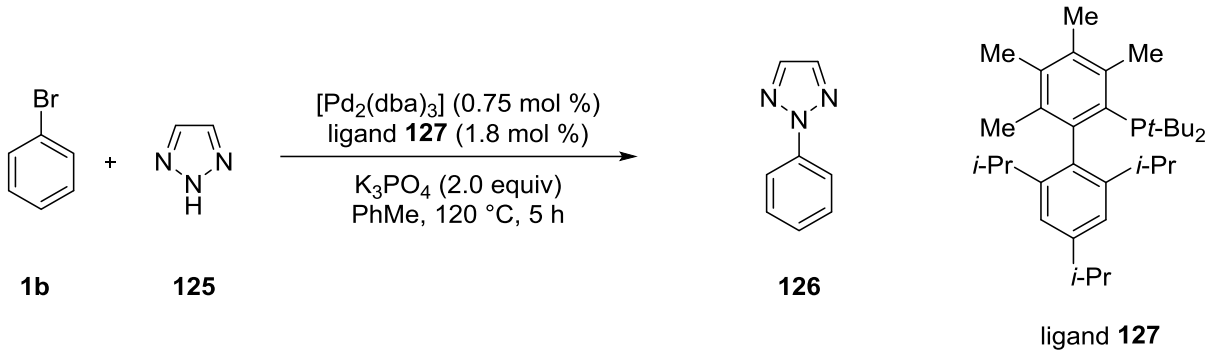
123 **1a** **124**

Scheme 1.46: Triazole assisted arylation.

[84] (a) J. Deng, Y.-M. Wu and Q.-Y. Chen, *Synthesis* **2005**, 2730−2738; (b) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333−2336.
[85] (a) L. Ackermann, R. Vicente and R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741−748; (b) L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem. Int. Ed.* **2009**, *48*, 201−204.
[86] L. Ackermann, R. Jeyachandran, H. K. Potukuchi, P. Novák, L. Büttner*, Org. Lett.* **2010***, 12*, 2056−2059.
[87] (a) L. Ackermann, S. Barfüßer, J. Pospech, *Org. Lett.* **2010***, 12*, 724−726. (b) L. Ackermann, R. Born, R. Vicente, *ChemSusChem* **2009**, 546−549*;* (c) L. Ackermann, R. Vicente, *Org. Lett.* **2009***, 11*, 4922-4925; (d) L. Ackermann, H. K. Potukuchi, D. Landsberg, R. Vicente, *Org. Lett.* **2008**, *10*, 3081-3084.

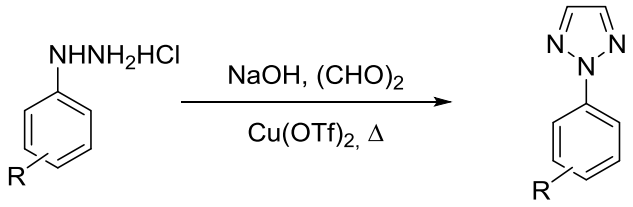
While the synthesis of 1-aryl-1,2,3-triazoles was largely described, the synthesis of 2-aryl-1,2,3-triazoles was studied less. Still some ways to synthesize these substrates were developed.

The first regioselective approach was published by *Buchwald* in 2011.[88] 2*H*-1,2,3-triazoles were arylated with either aryl bromides or chlorides with a palladium catalyst (Scheme 1.47).



Scheme 1.47: Palladium-catalyzed arylation of 2*H*-1,2,3-triazoles.

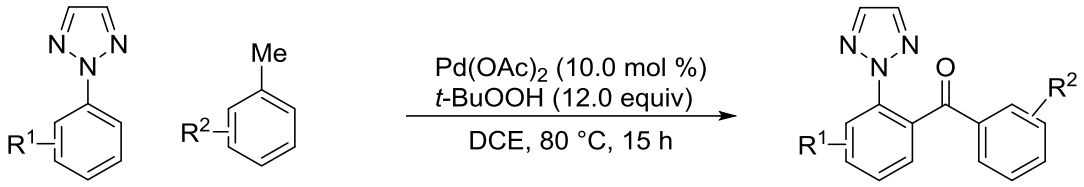
Mongin and co-workers reported the copper-catalyzed cyclization of glyoxal with (aryl)hydrazones (Scheme 1.48).[89]



Scheme 1.48: Copper-catalyzed synthesis of 2-aryl 1,2,3-triazoles.

Since the established synthesis of the core structures of 2*H*-1,2,3-triazoles, versatile functionalizations of these molecules were done. This includes the palladium-catalyzed halogenation, arylation, alkoxylation and acylation.[90] The acylation as representative C−H bond functionalization is shown in Scheme 1.49.[90d] The palladium-catalyzed acylation of 2*H*-1,2,3-triazoles worked with inexpensive toluene derivatives.

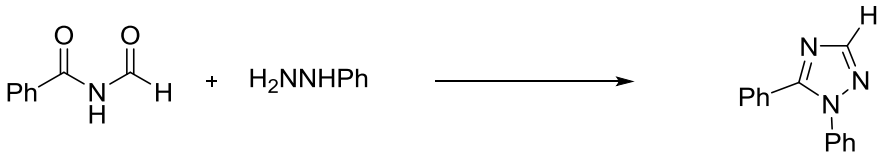
[88] S. Ueda, M. Su, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 8944–8947.
[89] F. Chevallier, T. Blin, E. Nagaradja, F. Lassagne, T. Roisnel, Y. S. Halauko, V. E. Matulis, O. A. Ivashkevichc, F. Mongin, *Org. Biomol. Chem.* **2012**, *10*, 4878–4885.
[90] Q. Tian, X. Chen, W. Liu, Z. Wang, S. Shi, C. Kuang, *Org. Biomol. Chem.* **2013**, *11*, 7830–7833; (b) S. Shi, W. Liu, P. He, C. Kuang, *Org. Biomol. Chem.* **2014**, *12*, 3576–3580; (c) S. Shi, C. Kuang, *J. Org. Chem*. **2014**, *79*, 6105−6112; (d) P. He, Q. Tian, C. Kuang, *Synthesis* **2015**, 1309–1316.



126 **4b** **129**

Scheme 1.49: Palladium-catalyzed acylation of 2-aryl 1,2,3-triazoles.

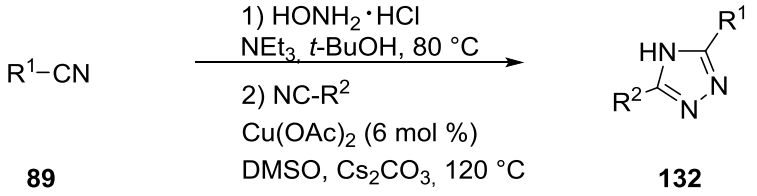
The synthesis of 1,2,3-triazoles was investigated by many research groups. However, the synthesis of 1,5-disubstituted 1,2,4-triazoles was studied less. The synthesis of the core structure could be obtained by condensation of phenylhydrazine with *N*-formylbenzamide to give the desired triazoles (Scheme 1.50).[91]



68d **130** **131**

Scheme 1.50: Condensation reaction to yield 1,5-disubstituted 1,2,4-triazoles.

An early transition metal-catalyzed synthesis of 1,2,4-triazoles was performed by *Nagasawa* in 2009.[92] Amidines were copper-catalyzed coupled with nitriles. Another access, directly using nitriles, was developed by *Ren*.[93] The copper-catalyzed synthesis of 1,2,4-triazoles by a one-pot reaction directly using nitriles is presented in Scheme 1.51.



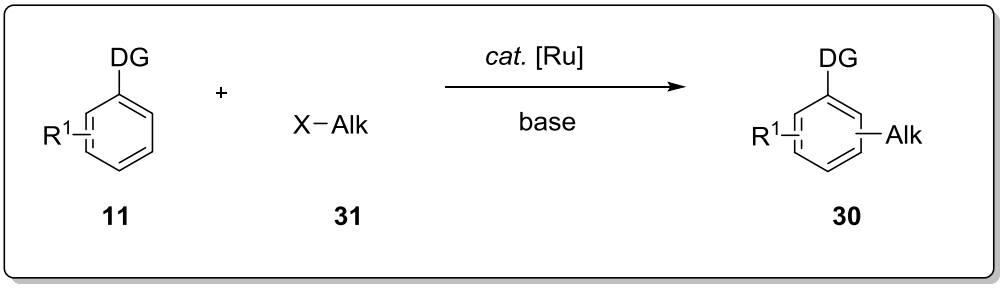
89 **132**

Scheme 1.51: Copper-catalyzed synthesis of 1,5-disubstituted 1,2,4-triazoles.

[91] Q. Thompson, *J. Am. Chem. Soc.* **1951**, *73*, 5914–5915.
[92] S. Ueda, H. Nagasawa, *J. Am. Chem. Soc.* **2009**, *131*, 15080–15081.
[93] H. Xu, S. Ma, Y. Xu, L. Bian, T. Ding, X. Fang, W. Zhang, Y. Ren, *J. Org. Chem.* **2015**, *80*, 1789−1794.

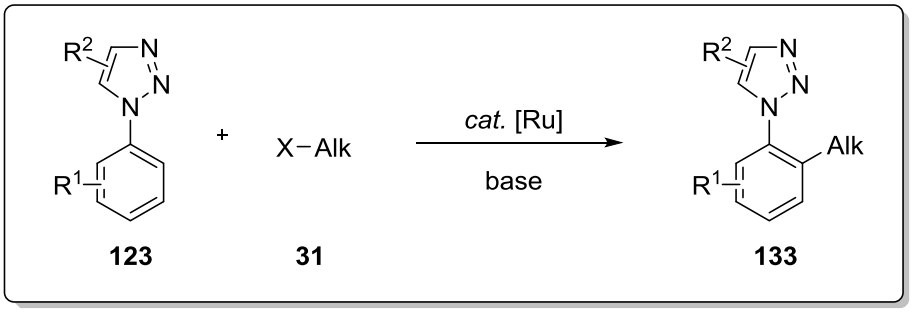
2 Objectives

Transition metal-catalyzed C−H bond functionalization emerged as an important topic of research in organic synthesis. These C−H bond functionalizations are step-economical methods for the preparation of chemo- and site-selectively arylated, alkenylated and alkylated products. They avoid the use of prefunctionalized starting materials as are needed, for example, in cross-coupling reactions. The key task of this thesis was the ruthenium(II)-catalyzed synthesis and functionalization of heterocyclic compounds. Thus recently, Prof. *Ackermann* and co-workers developed the direct alkylation reaction of aryl-pyridines, -pyrazoles and -ketimines with primary and secondary alkyl halides (Scheme 2.1).[27, 42, 94]



Scheme 2.1: Ruthenium(II)-catalyzed alkylation of arylpyridines, -pyrazoles and -ketimines.

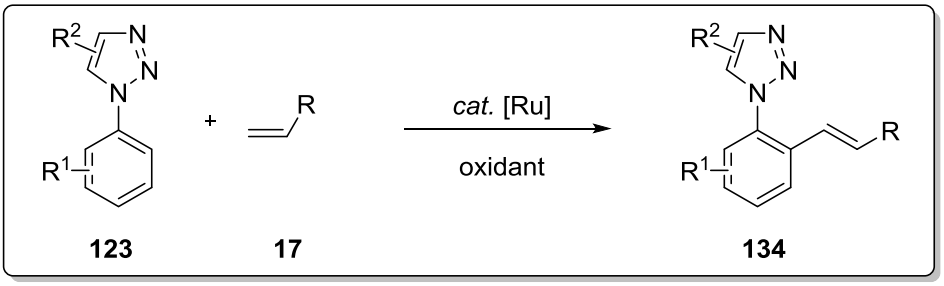
Herein we want to present the challenging alkylation of compounds bearing a triazole moiety, which is found in a variety of important pharmaceuticals and other valuable chemicals (Scheme 2.2).



Scheme 2.2: Ruthenium(II)-catalyzed alkylation of triazoles **123**.

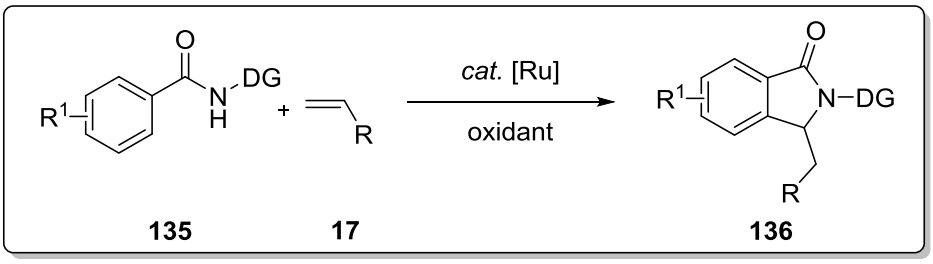
Further efforts focused on the extension of the ruthenium(II)-catalyzed alkenylation reactions of the aryl triazole (Scheme 2.3).

[94] L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13,* 1875−1877.



Scheme 2.3: Ruthenium(II)-catalyzed alkenylation of triazoles **123**.

Besides the ruthenium(II)-catalyzed functionalization of arenes with alkyl or aryl moieties, heterocyclic compounds were synthesized, mostly by annulation reactions with alkynes and alkenes.[56, 69-72] This part of the Ph.D. thesis adresses the development of a ruthenium(II)-catalyzed synthesis of isoindolinones **136** (Scheme 2.4).

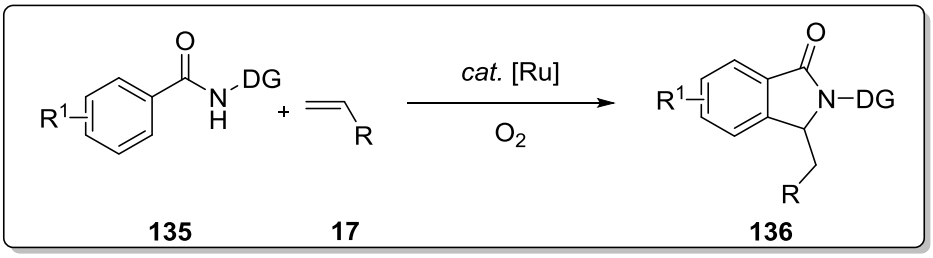


Scheme 2.4: Ruthenium(II)-catalyzed annulation of benzamides **135**.

Further investigations to provide mechanistic insights into this annulation reaction have also been envisaged.

The most ecological and atom-economic synthesis would proceed without producing side-products or chemical waste. Recently, major improvements in this field have been achieved by metal catalyzed synthesis.[53, 55a-b, 55d-e, 58, 95] Hence, the ruthenium(II)-catalyzed oxidative alkyne annulation of benzoic acids with molecular oxygen as the sole oxidant was developed in the Ackermann research group.[59]

Thus, the last challenging part comprised the use of the previously developed catalytic system with oxygen as the terminal oxidant for the isoindolinone synthesis.



Scheme 2.5: Ruthenium-catalyzed annulation of benzamides **135** with oxygen as sole oxidant.

[95] P. Zhao, D. Chen, G. Song, K. Han and X. Li, *J. Org. Chem.* **2012**, *77*, 1579−1584.

3 Results and Discussion

3.1 Ruthenium(II)-Catalyzed Direct Alkylation of *N*-Aryl-1,2,3-triazoles with *primary*-Bromoalkanes

Triazoles are key structural motifs of various compounds with significant relevance to biological and medicinal chemistry.[60] Drug potency and the drug bioavailability are the most important factors regarding drug effectiveness. Frequently, the drug potency is not the issue, but the lack of drug delivery. If the lipophilicity is high, the membrane permeability is improved, but some different problems occur, such as increasing the rate of oxidative metabolism by enzymes. Therefore, the lipophilicity of biologically active compounds has to be balanced carefully to improve the bioavailability.[96] The alkylation of biologically active molecules is one of the amenable ways to tune their lipophilicity. For this purpose, the direct metal-catalyzed C−H bond activation is an excellent tool, avoiding the pre-functionalized substrates, which are used in traditional cross-coupling reactions.

The ruthenium-catalyzed *ortho*-alkylations *via* C−H bond cleavage has primarily been examined by *Ackermann* et al. in 2009 using aryl pyridines and aromatic ketimines as substrates.[94a]

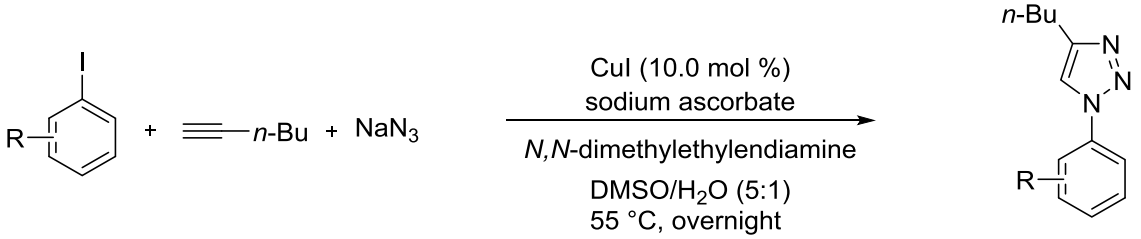
With respect to the significance of the triazole moiety[60] in drugs we investigated the alkylation reaction on *N*-aryl-1,2,3-triazoles.

3.1.1 Synthesis of Starting Materials

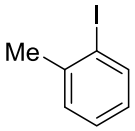
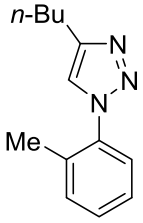
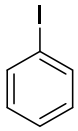
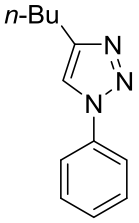
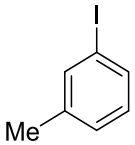
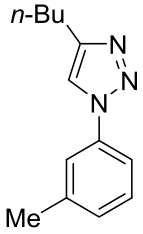
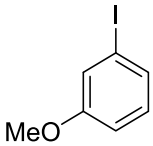
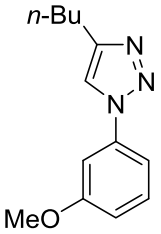
The starting materials, 1,4-disubstituted 1,2,3-triazoles were synthesized *via Huisgen*`s 1,3-dipolar [3+2] cycloaddition of azides and alkynes,[81] according to a literature-known procedure without optimization of the reaction conditions (Table 1).[97]

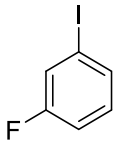
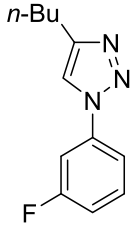
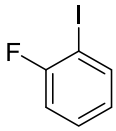
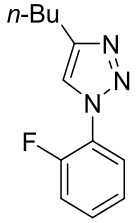
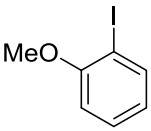
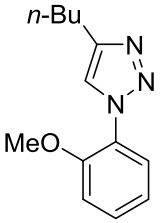
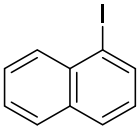
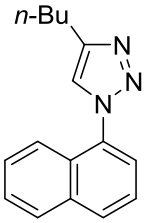
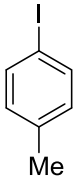
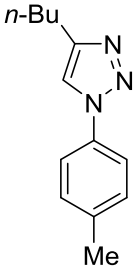
[96] M. Ambikanandan, S. Ganesh, S. Aliasgar, *J. Pharm. Pharmaceut Sci*. **2003**, *6*, 252−273.
[97] J. Andersen, S. Bolving, X. Liang, *Synlett* **2005**, 2941−2947.

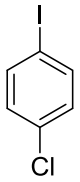
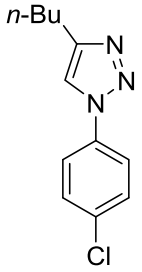
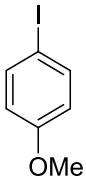
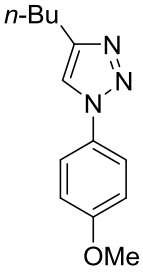
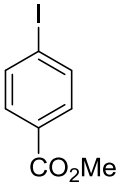
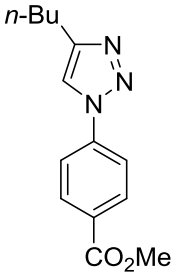
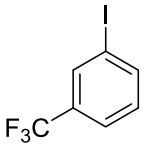
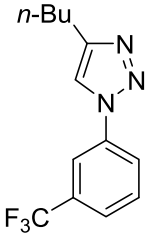
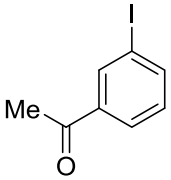
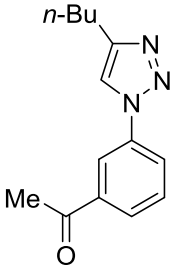
Table 1: Substrate scope of starting materials.[a]

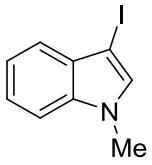
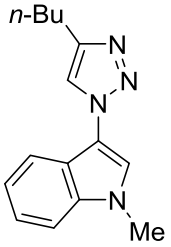


1c **81e** **123**

entry	substrate 1	product 123	yield [%]
1			63
	1d	**123a**	
2			78
	1e	**123b**	
3			63
	1f	**123c**	
4			93
	1g	**123d**	

5	 **1h**	 **123e**	88
6	 **1i**	 **123f**	86
7	 **1j**	 **123g**	89
8	 **1k**	 **123h**	80
9	 **1l**	 **123i**	76

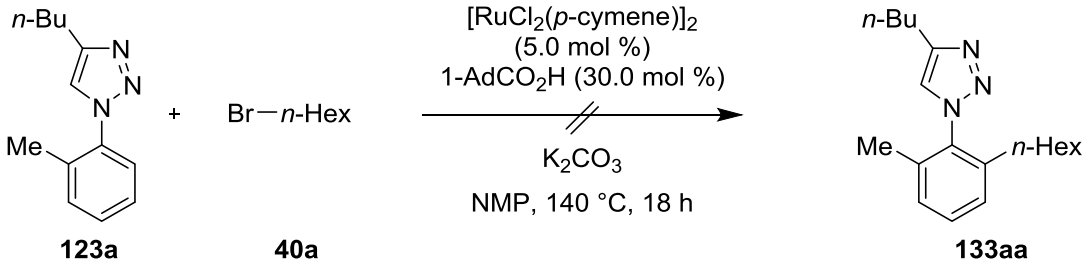
10	 **1m**	 **123j**	87
11	 **1n**	 **123k**	91
12	 **1o**	 **123l**	74
13	 **1p**	 **123m**	87
14	 **1q**	 **123n**	60

15			37
	1r	**123o**	

[a] General reaction conditions: **1c** (1.00 equiv), **81e** (1.00 equiv), NaN_3 (1.05 equiv), CuI (10.0 mol %), sodium ascorbate (10.0 mol %), *N,N*-dimethylethylendiamine (15.0 mol %), DMSO/H_2O (0.3 M), 55 °C, 12-15 h.

3.1.2 Optimization Studies for the C−H Alkylation of *N*-Aryl-1,2,3-triazoles with primary-Bromoalkanes

The ruthenium(II)-catalyzed *ortho*-alkylations *via* C−H bond activation have primarily been examined by *Ackermann* and co-workers.[40, 94b] An extensive screening of the reaction conditions established the *in-situ* generated catalytic system, using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and 1-adamantyl carboxylic acid as cocatalyst, to be most efficient. Using the established catalytic system to the triazole substrate **123a** with increased reaction temperature gave no conversion, of **123aa** (Scheme 3.1).

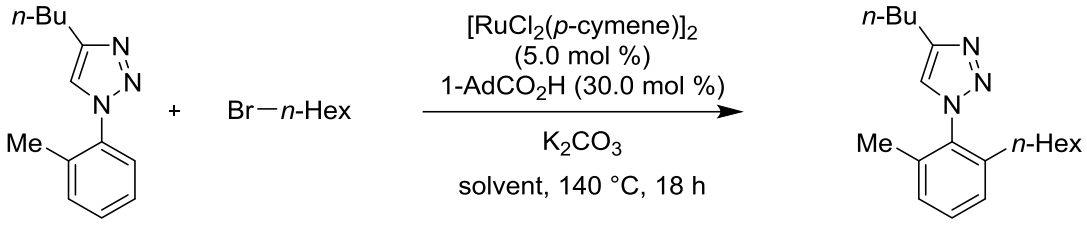


123a **40a** **133aa**

Scheme 3.1: Transferred reaction conditions[94b] on *N*-aryl-1,2,3-triazole **140a**.

Hence, an extensive screening of prosperous reaction conditions was applied, starting with investigations of different solvents and reaction temperatures (Table 2).

Table 2: Optimization studies for the direct alkylation of *N*-aryl-1,2,3-triazole **123a**: Solvent.[a]



123a **40a** **133aa**

entry	solvent	yield [%]
1	PhMe	(16)[b]
2	PhMe	20 (33)
3	NMP	(0)
4	NMP	(0)
5	DMSO	(0)
6	*o*-xylene	(10)
7	*m*-xylene	(20)
8	*n*-Bu_2O	(19)
9	H_2O	(0)
10	1,4-dioxane	(12)

[a] General reaction conditions: **123a** (1.00 mmol), **40a** (3.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5.0 mol %), 1-AdCO_2H (30.0 mol %), K_2CO_3 (2.00 mmol), solvent (4.0 mL), 18 h, isolated yield, yields in parentheses refer to NMR-conversion; [b] 110 °C.

Thus far, the yield of this reaction was very low. Furthermore, a notable conversion was observed in aprotic non-polar and polar solvents. The best isolated yield obtained was 20% in toluene as the solvent at 140 °C reaction temperature.

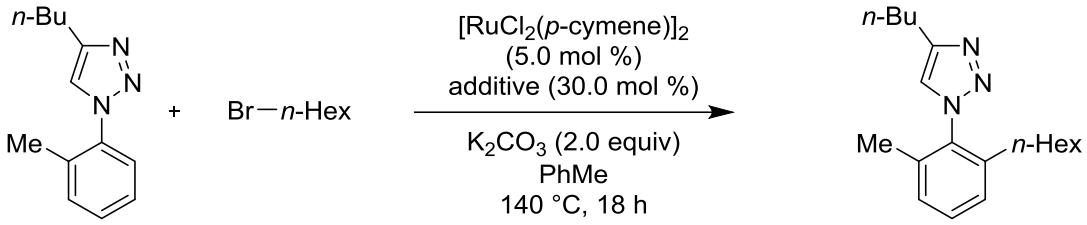
Extensive screening of different additives (Table 3) showed that a phosphine ligand resulted in no conversion (Table 3, entry 1). The use of the protected alanine resulted in no reaction. The usage of amino acids as ligands for palladium(II)-catalyzed C−H olefination was reported by *Yu*.[44e]

The use of aromatic carboxylic acids (Table 3, entries 5−16) revealed superior activity compared to non-aromatic carboxylic acids (Table 3, entries 2−4). The competition between the carboxylic acids and the potassium salts of the carboxylic acids revealed that the potassium salts used as additives resulted in higher yields than the corresponding carboxylic acids. The highest yield was obtained with potassium-4-(trifluoromethyl)benzoic carboxylate[98]

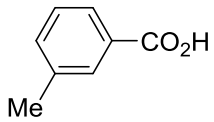
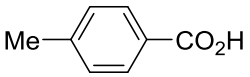
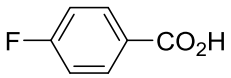
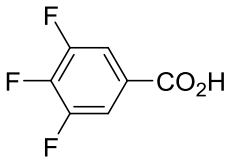
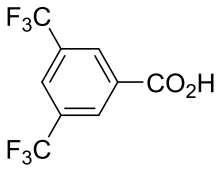
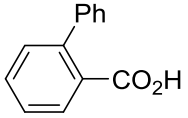
[98] F. Yang, L. Ackermann, *J. Org. Chem.* **2014**, *79*, 12070−12082.

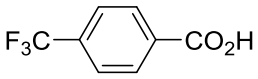
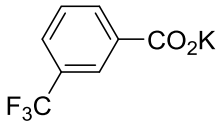
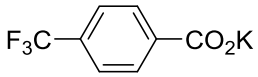
137 with 42% isolated yield (Table 3, entry 17). The comparison between electron poor and electron rich carboxylic acids as additives showed no correlation with regard to the product yield.

Table 3: Optimization studies for the direct alkylation of *N*-aryl-1,2,3-triazole **123a**: Additive.[a]



123a **40a** **133aa**

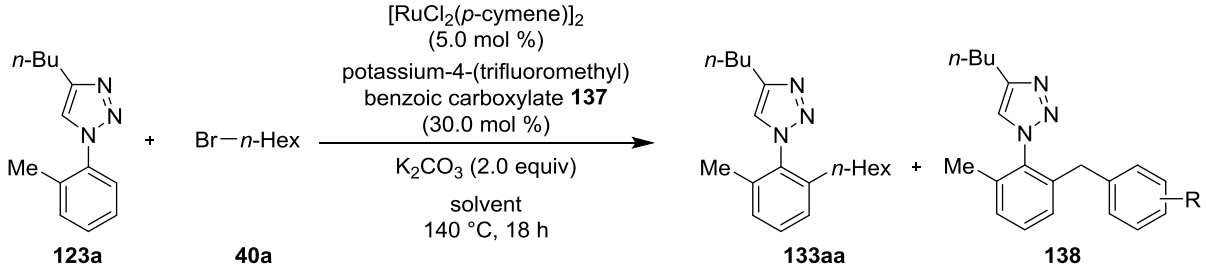
entry	Additive	yield [%]
1	PPh_3	0
2	*t*-$BuCO_2H$	0
3	*t*-$BuCO_2Cs$	28
4	Pivaloylalanine	0
5	1-$AdCO_2H$	23
6	1-$AdCO_2K$	33
7	$MesCO_2H$	0
8	$MesCO_2K$	31
9		31
10		25
11		29
12		18
13		20
14		28

15		32
16		24
17		42

[a] General reaction conditions: **123a** (1.00 mmol), **40a** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30.0 mol %), K_2CO_3 (2.00 mmol), PhMe (4.0 mL), 140 °C, 18 h, isolated yields.

In order to find out whether it was possible to establish a link between the additive and the solvent, different solvents were tested with potassium-4-(trifluoromethyl)benzoic carboxylate **137** (Table 4). Unfortunately, the solvent screening showed no improvement. Furthermore, we observed the formation of a benzylated by-product in toluene (**138a**, 16%) and in *m*-xylene (**138b**, 5%), reducing the amount of the desired alkylated product. Neat reaction conditions with an excess of bromohexane afforded no product.

Table 4: Optimization studies for the direct alkylation of *N*-aryl-1,2,3-triazole **123a**: Solvent with additive **137**.[a]



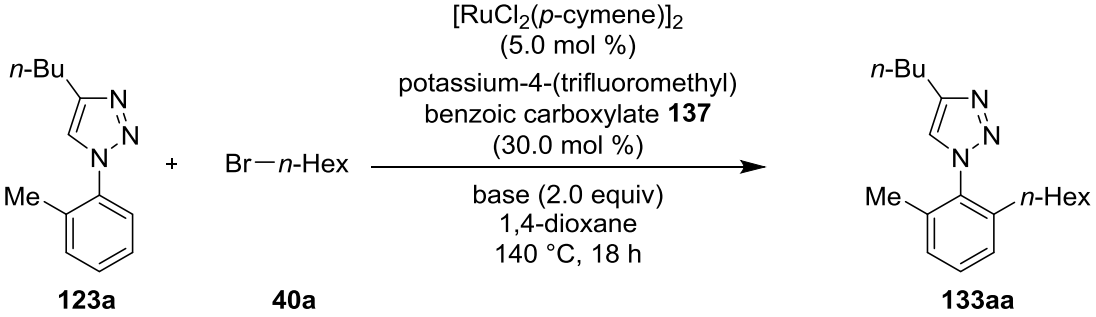
123a **40a** **133aa** **138**

entry	solvent	yield 133 [%]	yield 138 [%]
1	PhMe	42	16
2	*m*-xylene	20	5
3	H_2O	---	---
4	1,4-dioxane	35	---
5	-	---[b]	---

[a] General reaction conditions: **123a** (1.00 mmol), **40a** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), potassium-4-(trifluoromethyl)benzoic carboxylate (30.0 mol %), K_2CO_3 (2.00 mmol), solvent (4.0 mL), 140 °C, 18 h, isolated yields; [b] **40a** (5.00 mmol).

Next, we tested different bases, using the best additive **137** in 1,4-dioxane (Table 5) with different carbonates or K_3PO_4 as the base the yields remained comparably low (Table 5, entry 1−4). When KOAc was used as the base, the yield dropped significantly (Table 5, entry 5).

Table 5: Optimization studies for the direct alkylation of *N*-aryl-1,2,3-triazole **123a**: base.[a]



123a **40a** **133aa**

entry	base	yield [%]
1	KOAc	6
2	Na_2CO_3	36
3	Cs_2CO_3	24
4	K_3PO_4	37
5	K_2CO_3	35
6	K_2CO_3	11[b]
7	K_2CO_3	18[b,c]
8	K_2CO_3	trace[c,d]
9	K_2CO_3	32[e]

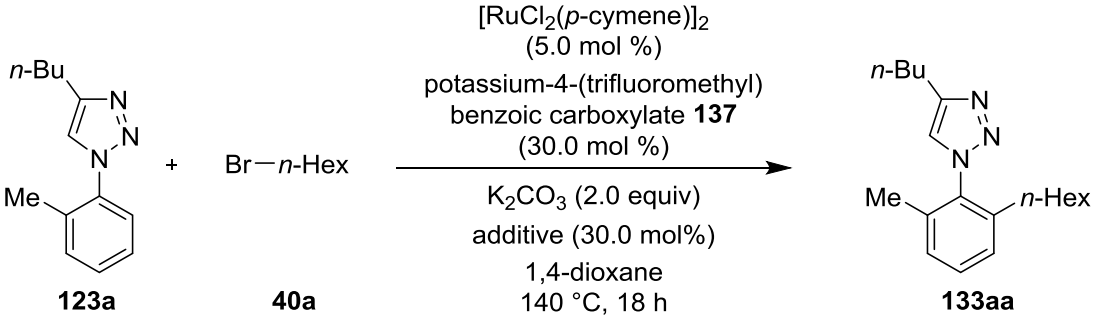
[a] General reaction conditions: **123a** (1.00 mmol), **40a** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), potassium-4-(trifluoromethyl)benzoic carboxylate (30.0 mol %), base (2.00 mmol), 1,4-dioxane (4.0 mL), 140 °C, 18 h, isolated yields; [b] I−*n*-Hex (3.00 mmol); [c] PhMe; [d] Cl−*n*-Hex (3.00 mmol); [e] NaI (30.0 mol%).

When changing the 1-bromohexane to 1-iodohexane (Table 5, entry 6 and 7), the amount of the desired product did not increase. Testing the much less reactive and less expensive chlorohexane led to no conversion. The *in situ* generation of the 1-iodohexane *via* the *Finkelstein* reaction using sodium iodide as the additive resulted in a comparable yield (Table 5, entry 9).

To probe if cationic complexes give higher amounts of the desired product, several further additives were tested (Table 6). Silver hexafluoroantimonate and silver hexafluorophosphate completely shut down the reaction. The presence of silver tetrafluoroborate and potassium hexafluorophosphate gave similar yields to the reaction without additive. In conclusion,

cationic complexes are probably not involved in the present catalytic system and do not improve the reactivity of the catalyst. As a consequence we did not test further additives.

Table 6: Optimization studies for the direct alkylation of *N*-aryl-1,2,3-triazole **123a**: Second additives.[a]



123a **40a** **133aa**

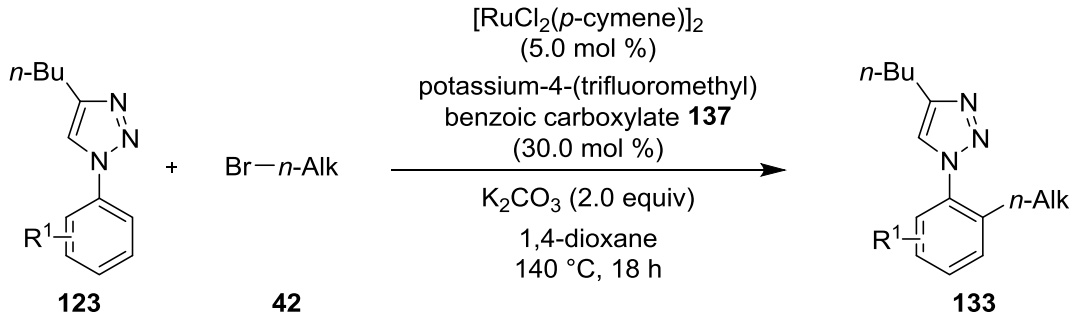
entry	additive	yield [%]
1	-	35
2	$AgSbF_6$	0
3	$AgPF_6$	trace
4	$AgBF_4$	36
5	KPF_6	39

[a] General reaction conditions: **123a** (1.00 mmol), **40a** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), **137** (30.0 mol %), K_2CO_3 (2.00 mmol), 1,4-dioxane (4.0 mL), 140 °C, 18 h, isolated yields.

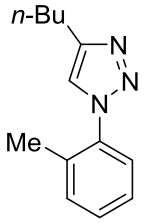
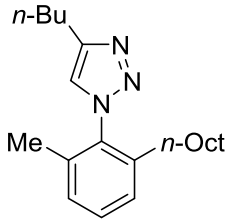
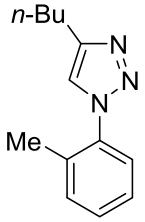
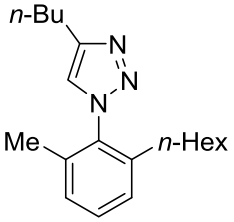
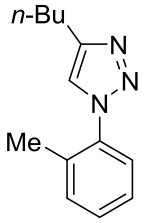
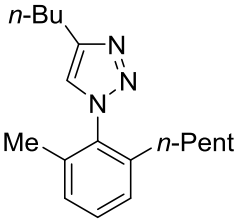
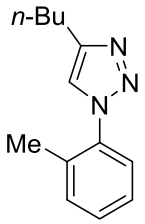
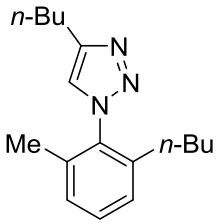
3.1.3 Scope and Limitations for the C−H Alkylation of *N*-Aryl-1,2,3-triazoles with Alkyl Bromides

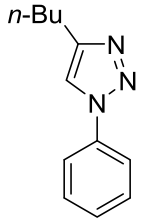
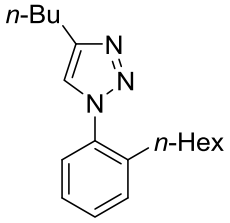
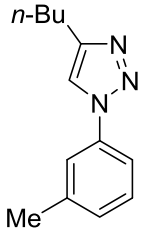
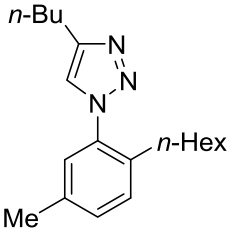
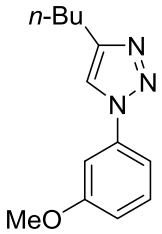
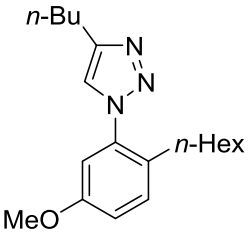
With the best catalytic system in hand, we explored different alkyl bromides **40** to figure out if the length of the alkyl chain has an influence on the catalytic reaction (Table 7). However, an effect on the reaction was not observed (Table 7, entry 1−4). Next, different triazole substrates **123** were investigated. The unsubstituted compound **123b** afforded a comparable yield of product (entry 5), while substituents in the *meta*-position decreased the yield (Table 7, entry 6−7). The *meta*-methoxy group (Table 7, entry 7) demonstrated that electron-rich substrates gave low yields.

Table 7: Substrate scope for the alkylation of *N*-aryl-1,2,3-triazoles **123**.[a]



123 **42** **133**

entry	substrate 123	bromide 40	product 133	yield [%]
1	 **123a**	Br—*n*-Oct	 **133ab**	41
2	 **123a**	Br—*n*-Hex	 **133aa**	42[b]
3	 **123a**	Br—*n*-Pent	 **133ac**	37
4	 **123a**	Br—*n*-Bu	 **133ad**	42

5		Br—*n*-Hex		39
	123b	**40a**	**133ba**	
6		Br—*n*-Hex		25
	123c	**40a**	**133ca**	
7		Br—*n*-Hex		---
	123d	**40a**	**133da**	

[a] General reaction conditions: **123** (1.00 mmol), **40** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), **137** (30.0 mol %), K_2CO_3 (2.00 mmol), 1,4-dioxane (4.0 mL), 140 °C, 18 h, isolated yields; [b] PhMe.

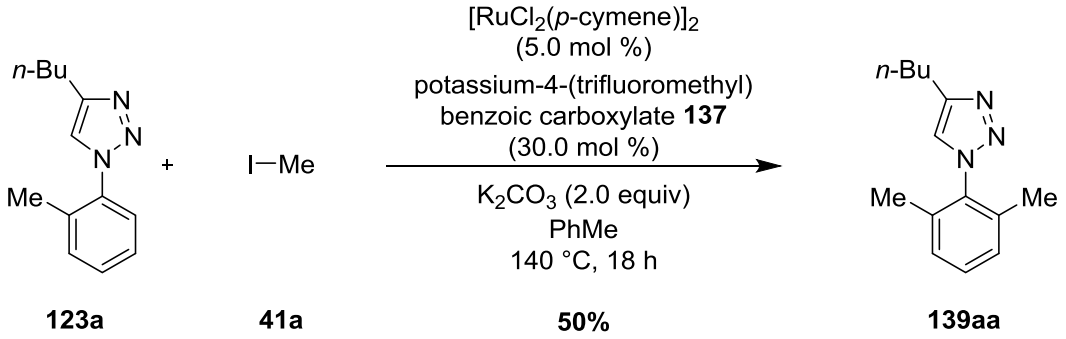
Because only moderate yields were obtained, we went on to explore other alkylating reagents. Some improvement could be possibly made by eliminating the benzylated side-product, which is formed using toluene as the solvent. The means of solving this, could lie in interchanging the ratio of the triazole and the primary alkyl bromides. Another problem was found to be related to the esterification of the carboxylic acid additive **137** with the alkyl bromide **40**. Thus, by suppressing either of these side-reactions could improve the reaction yield afterall.

Given the challenge in alkylation reactions with alkyl bromides bearing a longer chain, we hypothesized there might be some improvement by replacing the chain by a simple methyl group. These considerations led to the second part of this project on alkylation, the methylation of *N*-aryl-1,2,3-triazoles.

3.2 Ruthenium(II)-Catalyzed C−H Methylation of *N*-Aryl-1,2,3-triazoles

3.2.1 Optimization Studies and Scope for the C−H Methylation of *N*-Aryl-1,2,3-triazoles

We were delighted to observe, that the methylation worked with good yield using the reaction conditions developed for the alkylation of the *N*-aryl-1,2,3-triazoles with alkyl bromides (Scheme 3.2).



123a **41a** **50%** **139aa**

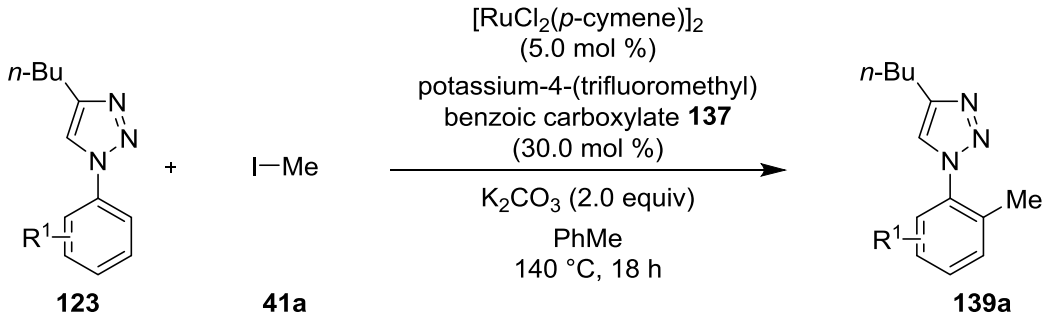
Scheme 3.2: Reaction conditions for the C−H alkylation of *N*-aryl-1,2,3-triazole **123a**.

Furthermore, different reaction set ups were performed. First, we considered methyl 4-methylbenzenesulfonate as an inexpensive methylation reagent, which was first applied by *Gong*,[99] but no reaction occurred (Table 8, entry 3).
Second, we set up the reaction in an microwave oven at 50 W for 24 h. This resulted in a complex mixture of different products.
In order to exclude the effect of oxygen on the reaction, degassed toluene was used, leading as well to unidentified methylated by-products. The starting material **123a** could be still observed by crude NMR. To guarantee an inert reaction atmosphere, the reaction was set up in the glovebox, successfully giving constant amounts of product. The reaction was performed twice with an average yield of 55% of the desired product (Table 8, entry 4).

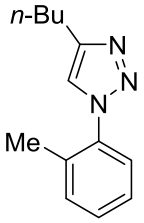
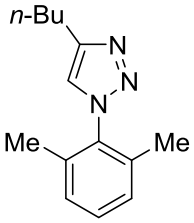
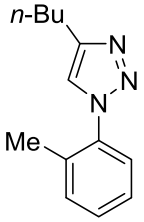
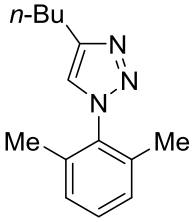
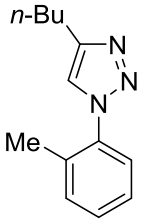
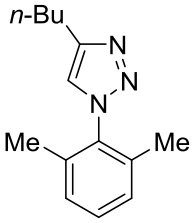
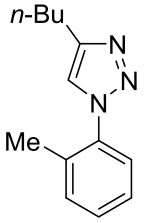
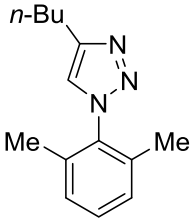
When changing the methyl substituent of the triazole to a fluoro substituent, the benzylated by-product was noticed again. Switching to 1,4-dioxane as the solvent the desired product could be obtained in 70% isolated yield (entry 6). Interestingly, the substrate bearing an electron donating methoxy group (entry 7) gave no reaction.

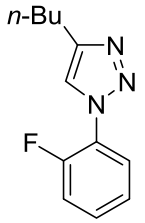
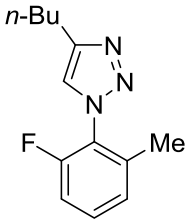
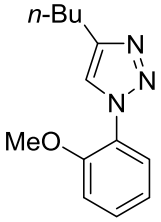
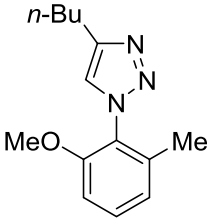
[99] Z. Liang, W. Xue, K. Lin, H. Gong, *Org. Lett.* **2014**, *16*, 5620−5623.

Table 8: Different reaction set ups for the methylation of *N*-aryl-1,2,3-triazoles **123**.[a]



123 **41a** **139a**

entry	substrate 123	product 139	yield [%]
1	 **123a**	 **139aa**	50[b]
2	 **123a**	 **139aa**	---[c]
3	 **123a**	 **139aa**	55[b,d]
4	 **123a**	 **139aa**	(30)[b.d]

5	 **123f**	 **139fa**	70[d,e]
6	 **123g**	 **139ga**	---[d,e]

[a] General reaction conditions: **123** (1.00 mmol), **41a** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), **137** (30.0 mol %), K_2CO_3 (2.00 mmol), PhMe (4.0 mL), 140 °C, 18 h, isolated yields, yields in parentheses refer to NMR-conversion; [b] average of two reactions; [c] MeOTs (3.00 mmol); [d] set up in the glovebox; [e] 1,4-dioxane.

Due to the severe limitations we decided not to pursue this project any further. Still interested in the triazole substrates, because of their widespread application and inspired by the recently published patent, which describes the use of several alkenylated *N*-aryl-1,2,3-triazoles to treat thrombotic diseases,[100] we focused on developing a methodology for the C−H alkenylation of these derivatives.

[100] US|PCT/US2006/062005|ArylpropionaMIDE; Arylacrylamide; Arylpropynamide, or Arylmethylurea analogs As Factor XIA inhibitors|21 June 2007|P. Donald, J. M. Smallheer, Z. Hu, C. L. Cavallaro, P. J. Gilligan, M. L. Quan.

3.3 Ruthenium(II)-Catalyzed Oxidative C−H Alkenylation of *N*-Aryl-1,2,3-triazoles with Acrylates

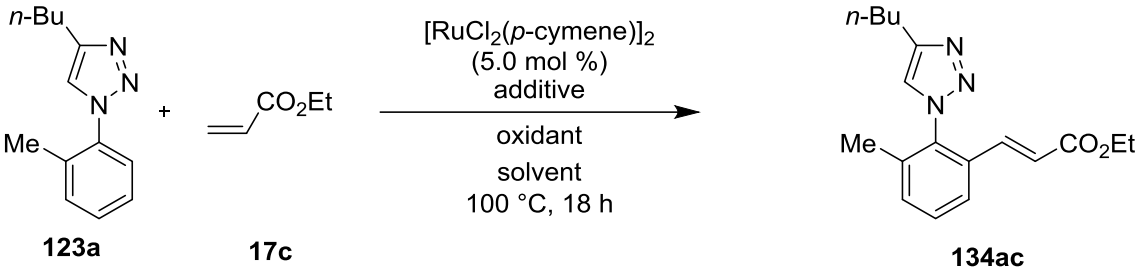
3.3.1 Optimization Studies for the C−H Alkenylation of *N*-Aryl-1,2,3-triazoles with Acrylates

Recently, major progress in the development of various *Fujiwara-Moritani*-type ruthenium-catalyzed oxidative C−H alkenylation reactions has been done by the *Ackermann* research group and others.[47a, 48b, 87a, 101] Because of this, the optimization studies of the direct alkenylations of triazoles started with the most common approach for direct alkenylations. Using copper acetate monohydrate as the oxidant and silver hexafluoroantimonate as the additive in toluene yielded the alkenylated product **134** in very good yield on the first attempt. Several other additives (Table 9, entry 1−7) were tested in the optimization studies (Table 9). Without any additive (Table 9, entry 1) as well as with acetates (Table 9, entry 2) or potassium hexafluorophosphate (Table 9, entry 3) as additives, a reaction did not occur. The different silver salts and counteranions gave comparable yields, except for the weakly coordinating anion $Ag[Al(OC\{CF_3\}_3)_4]$[102] (Table 9, entry 6), which gave only moderate yield.
Investigations of different reaction conditions revealed that the established $[RuCl_2(p\text{-cymene})]_2$ complex worked better than the carboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ **140**. Without catalyst there was no product formation. The crucial temperature for this reaction was 100 °C. Outstandingly, the catalytic system was found to be air stable (Table 9, entry 11). Replacing the copper acetate monohydrate by silver acetate or manganese acetate decreased or shut down the oxidative alkenylation (Table 9, entry 12−13). The reaction could be performed in various solvents (Table 9, entry 13−16).

[101] Selected recent examples of oxidative ruthenium-catalyzed C−H alkenylations: a) X. G. Li, M. Sun, K. Liu, P. N. Liu Adv. *Snth. Catal.* **2014**, *357,* 395−399; b) J. Li, M. John, L. Ackermann, *Chem. Eur. J*. **2014**, *20*, 5403–5408; c) M. C. Reddy, M. Jeganmohan, *Eur. J. Org. Chem*. **2013**, *2013*, 1150–1157; d) W. Ma, L. Ackermann, *Chem. Eur. J.* **2013**, *19,* 13925–13928; e) S. R. Chidipudi, M. D. Wieczysty, I. Khan, H. W. Lam, *Org. Lett.* **2013**, *15*, 570–573; f) M. C. Reddy, M. Jeganmohan, *Eur. J. Org. Chem*. **2013**, 1150–1157; g) K. S. Singh, P. H. Dixneuf, *Organometallics*, **2012**, *31*, 7320–7323; h) J. Li, C. Kornhaaß, L. Ackermann, *Chem. Commun.* **2012**, *48*, 1134–11345; i) B. Li, K. Devaraj, C. Darcel, P. H. Dixneuf, *Green Chem*. **2012**, *14*, 2706–2709; j) B. Li, J. Ma, N. Wang, H. Feng, S. Xu, B. Wang, *Org. Lett*. **2012**, *14*, 736–739; k) R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun*. **2012**, *48*, 3030–2032.

[102] U. Preiss, I. Krossing, *Z. Anorg. Allg. Chem*. **2007**, *633*, 1639−1644.

Table 9: Optimization studies for the oxidative C−H alkenylation of *N*-aryl-1,2,3-triazole **123a**.[a]



123a **17c** **134ac**

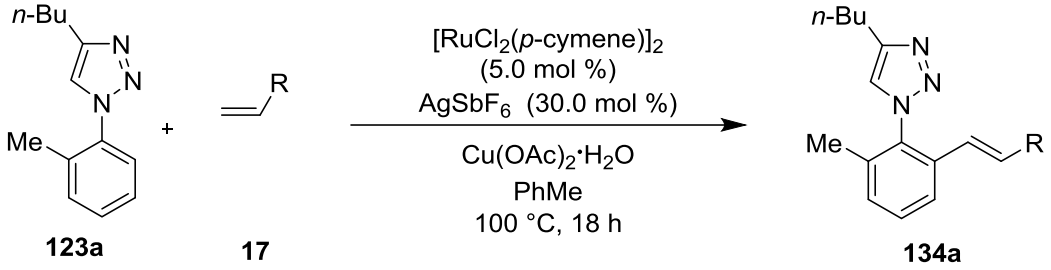
entry	solvent	additive	oxidant	yield (%)
1	PhMe	-	$Cu(OAc)_2 \cdot H_2O$	---
2	PhMe	NaOAc	$Cu(OAc)_2 \cdot H_2O$	---
3	PhMe	KPF_6	$Cu(OAc)_2 \cdot H_2O$	---
4	PhMe	$AgPF_6$	$Cu(OAc)_2 \cdot H_2O$	75
5	PhMe	$AgBF_4$	$Cu(OAc)_2 \cdot H_2O$	83
6	PhMe	$Ag[Al(OC\{CF_3\}_3)_4]$	$Cu(OAc)_2 \cdot H_2O$	63
7	PhMe	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	82
8	PhMe	$AgSbF_6$	-	---
9	PhMe	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	---[b]
10	PhMe	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	46[c]
11	PhMe	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	56[d]
12	PhMe	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	69[e]
13	PhMe	$AgSbF_6$	AgOAc	55
14	PhMe	$AgSbF_6$	$Mn(OAc)_2$	5
15	PhMe	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	85[f]
16	H_2O	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	58[f]
17	*t*-AmOH	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	74[f]
18	*m*-xylene	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	89[f]

[a] General reaction conditions: **123a** (1.00 mmol), **17c** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30.0 mol %), oxidant (1.20 mmol), solvent (4.0 mL), 100 °C, 18 h, yields of isolated products; [b] no catalyst; [c] T = 80 °C; [d] $[Ru(O_2CMes)_2(p\text{-cymene})]$ **140** (5.0 mol %); [e] under air (1 atm); T = 140 °C.

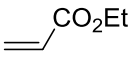
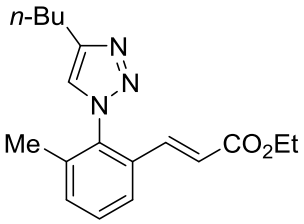
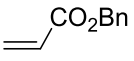
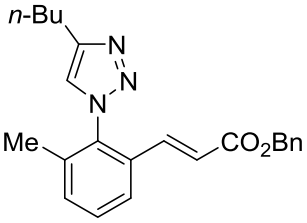
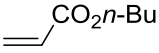
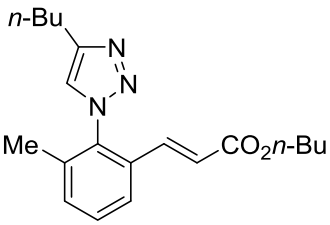
3.3.2 Scope and Limitations for the Direct Alkenylation of *N*-Aryl-1,2,3-triazoles with Acrylates

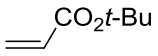
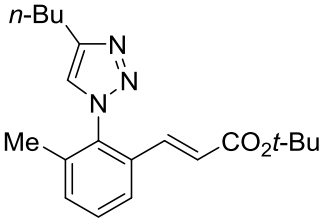
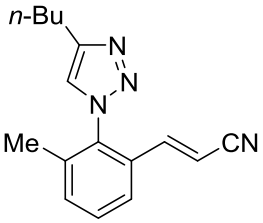
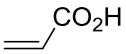
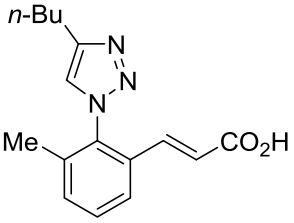
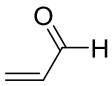
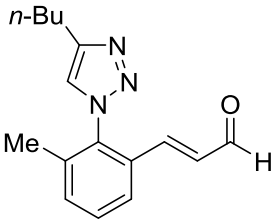
With the optimized conditions in hand, we explored the substrate scope and therefore tested different alkenes **17** (Table 10). While ethyl acrylate **17c** gave the highest amount of product (82%), the yield dropped as the steric bulk of the ester substituent increased (Table 10, entry 2-4). In contrast, when using acrylonitrile, acrylic acid or acroleine, there was only poor or no conversion (Tabele 10, entry 5−7).

Table 10: Substrate scope for oxidative alkenylations of 4-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole **123a**.[a]



123a **17** **134a**

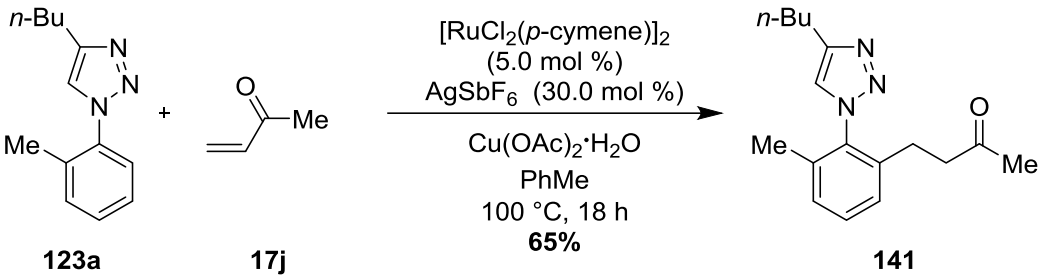
entry	alkene 123	product 134	yield [%]
1			82
	17c	**134ac**	
2			68
	17d	**134ad**	
3			67
	17e	**134ae**	

4			65
	17f	**134af**	
5			15
	17g	**134ag**	
6			trace
	17h	**134ah**	
7			---
	17i	**134ai**	

[a] General reaction conditions: **123a** (1.00 mmol), **17** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.20 mmol), PhMe (4.0 mL), 100 °C, 18 h, yields of isolated products.

Not surprisingly, we obtained the alkylated product *N*-aryl-1,2,3-1*H*-triazole **141**, by using methylvinylketone in 65% yield (Scheme 3.3). This is in accordance to the previous work regarding alkylations with *α,β*-unsaturated ketones.[103]

[103] a) G. Rouquet, N. Chatani, *Chem. Sci*. **2013**, *4*, 2201–2208; b) L. Yang, B. Qian, H. Huang, *Chem. Eur. J.* **2012**, *18*, 9511−9515; c) L. Yang, C. Correia, C. Li, *Org. Biomol. Chem.* **2011**, *9*, 7176−7179; d) Y. Kuninobu, Y. Nishina, K. Okaguchi, M. Shouho, K. Takai, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1393−1401.

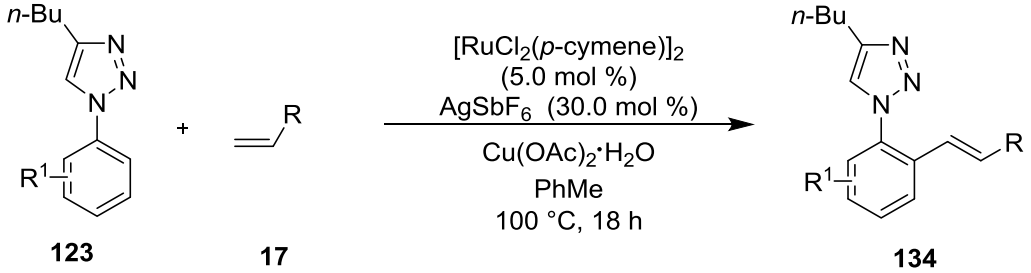


123a **17j** **141**

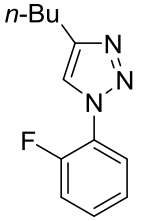
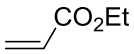
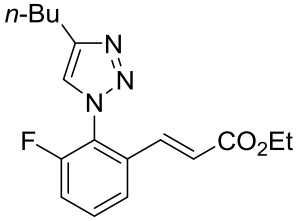
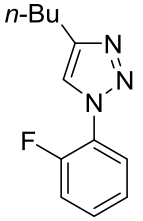
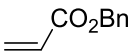
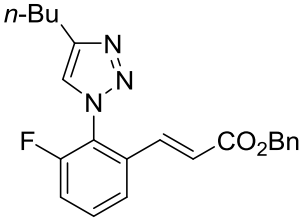
Scheme 3.3: C−H alkylation with methylvinylketone **17j.**

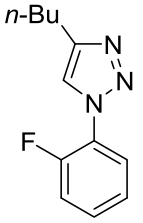
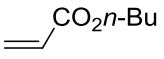
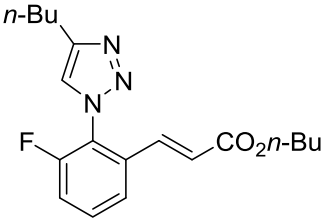
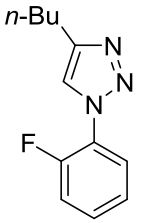
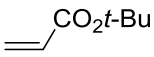
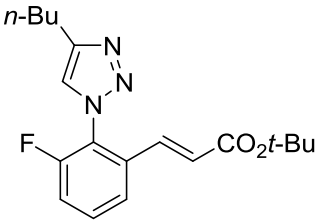
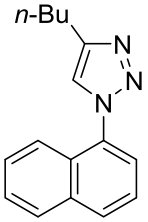
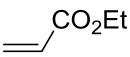
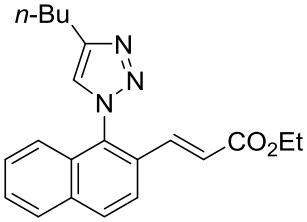
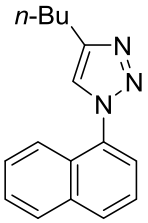
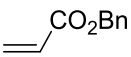
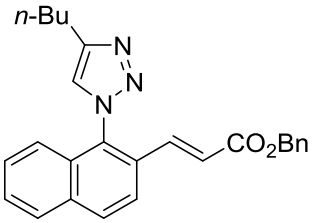
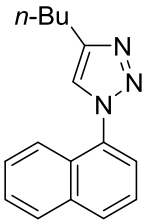
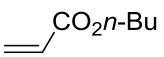
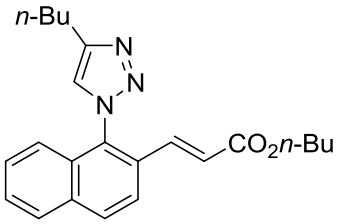
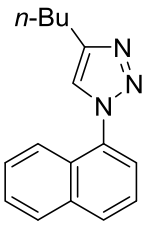
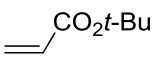
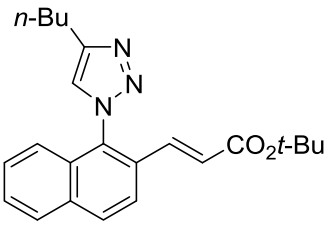
Next, we studied the influence of the different substituents on the *N*-aryl-1,2,3-triazoles **123** on the reaction efficacy. We were pleased to observe that the catalyst proved to be broadly applicable and, hence, furnished the desired products **134** in moderate to good yields (Table 11).

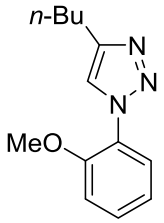
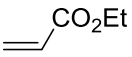
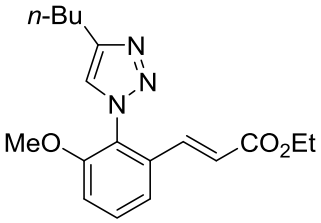
Table 11: Substrate scope for oxidative alkenylations of *ortho*-substituted *N*-aryl-1,2,3-triazoles **123**.[a]



123 **17** **134**

entry	substrate 123	alkene 17	product 134	yield [%]
1				60
	123f	**17c**	**134fc**	
2				79
	123f	**17d**	**134fd**	

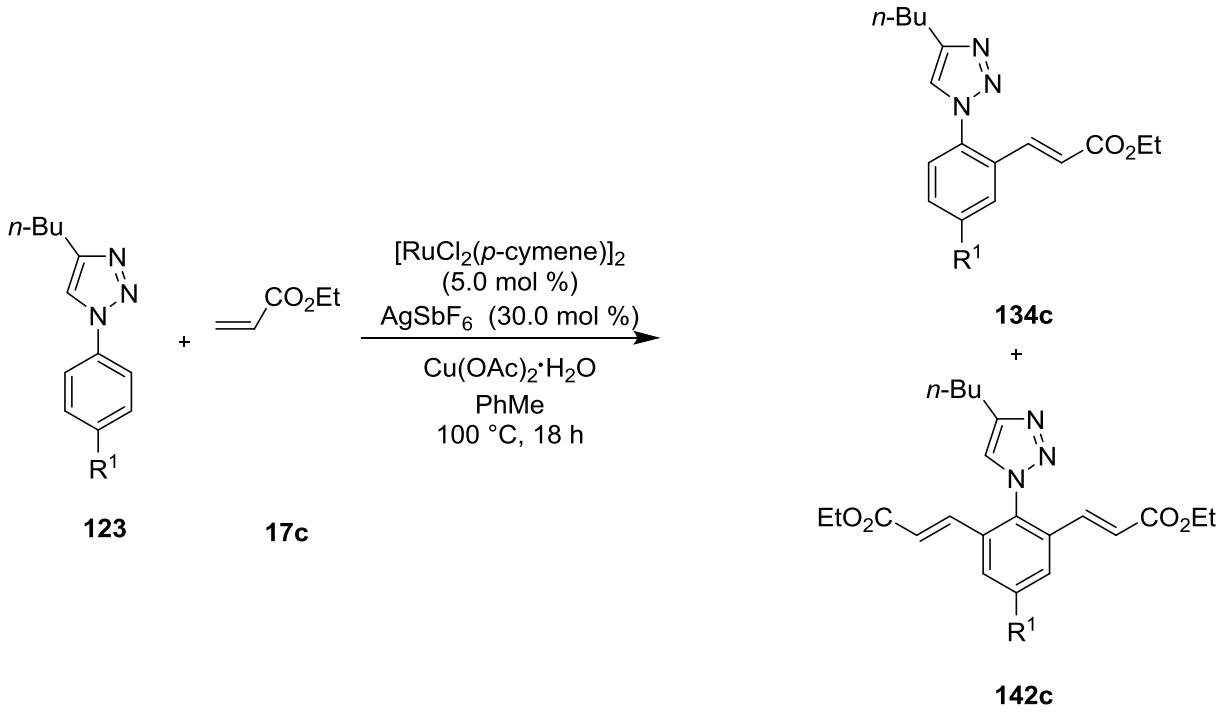
3	 **123f**	 **17e**	 **134fe**	76
4	 **123f**	 **17f**	 **134ff**	56
5	 **123h**	 **17c**	 **134hc**	58
6	 **123h**	 **17d**	 **134hd**	70
7	 **123h**	 **17e**	 **134he**	71
8	 **123h**	 **17f**	 **134hf**	72

9				53
	123g	**17c**	**134gc**	

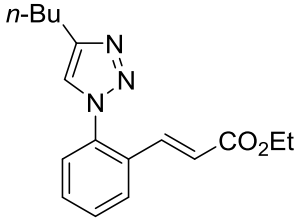
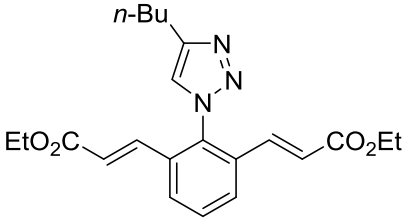
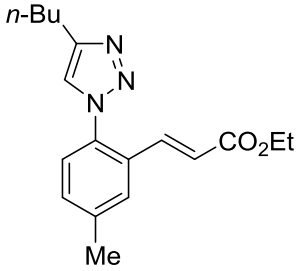
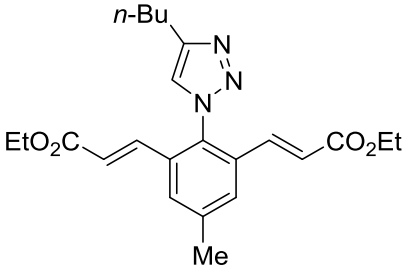
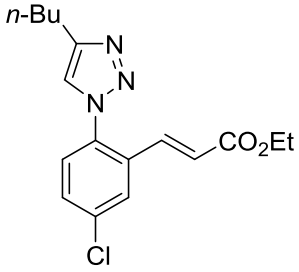
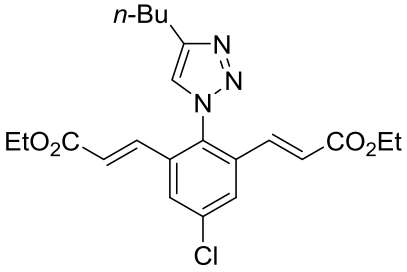
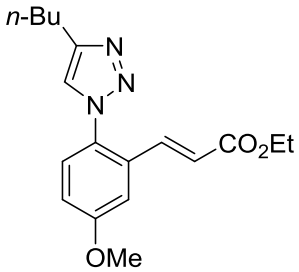
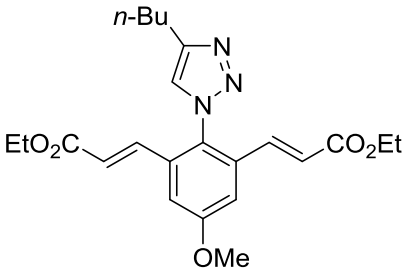
[a] General reaction conditions: **123** (1.00 mmol), **17** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.20 mmol), PhMe (4.0 mL), 100 °C, 18 h, yields of isolated products.

By applying the optimal reaction conditions on 4-butyl-1-phenyl-1*H*-1,2,3-triazole **123b** and *para*-substituted *N*-aryl-1,2,3-triazoles **123** the yield decreased significantly (Table 12). Moreover, the problem of the double C−H alkenylation emerged.

Table 12: Substrate scope for alkenylations of the unsubstituted **123b** and *para*-substituted *N*-aryl-1,2,3-triazoles **123**.[a]



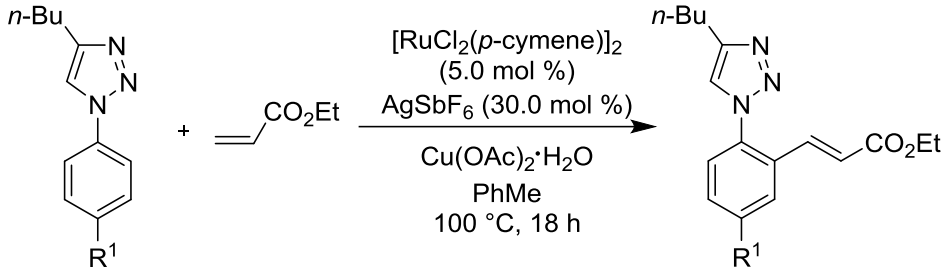
123 **17c** **134c** + **142c**

entry	substrate 123	product 134	yield [%]	product 142	yield [%]
1	R^1 = H		39		4
	123b	**134bc**		**142bc**	
2	R^1 = Me		46		7
	123i	**134ic**		**142ic**	
3	R^1 = Cl		44		---
	123j	**134jc**		**142jc**	
4	R^1 = OMe		55		---
	123k	**134kc**		**142kc**	

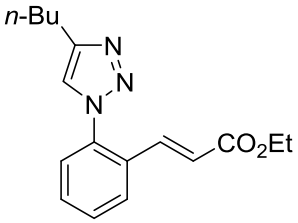
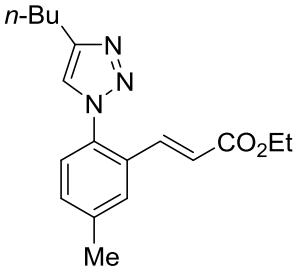
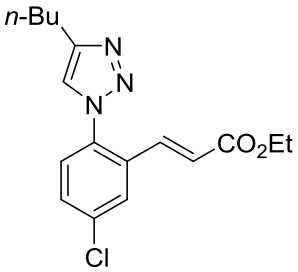
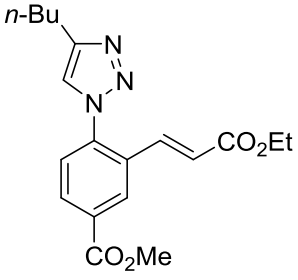
[a] General reaction conditions: **123** (1.00 mmol), **17c** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.20 mmol), PhMe (4.0 mL), 100 °C, 18 h, yields of isolated products.

The usual way to suppress the double C−H alkenylation is interchanging the ratio between the acrylate and the *N*-aryl-1,2,3-triazoles **123**. We tried this for several substrates (Table 13), but the results are largely unsatisfactory. The amount of product formed for the different substrates was low, but the double alkenylated products could not be observed.

Table 13: Substrate scope for oxidative alkenylations with excess of the unsubstituted **123b** and *para*-substituted *N*-aryl-1,2,3-triazoles **123**.[a]



123 **17c** **134**

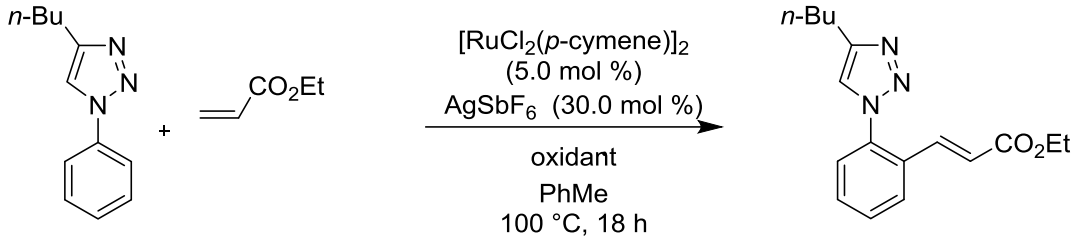
entry	substrate 123	product 134	yield [%]
1	R^1 = H		33
	123b	**134bc**	
2	R^1 = Me		40
	123i	**134ic**	
3	R^1 = Cl		26
	123j	**134jc**	
4	R^1 = CO_2Me		---

123l	**134lc**

[a] General reaction conditions: **123** (1.00 mmol), **17c** (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.60 mmol), PhMe (2.0 mL), 100 °C, 18 h, yields of isolated products.

As a consequence, we undertook a new screening and the amount of acrylate was doubled. Hence, we were pleased to observe that the reaction worked even better under air. The use of other oxidants like silver acetate, silver carbonate and copper acetate resulted in a lower yield (Table 14).

Table 14: Optimization studies for the direct alkenylation of 4-butyl-1-phenyl-1*H*-1,2,3-triazole **123b**: oxidant and atmosphere.[a]



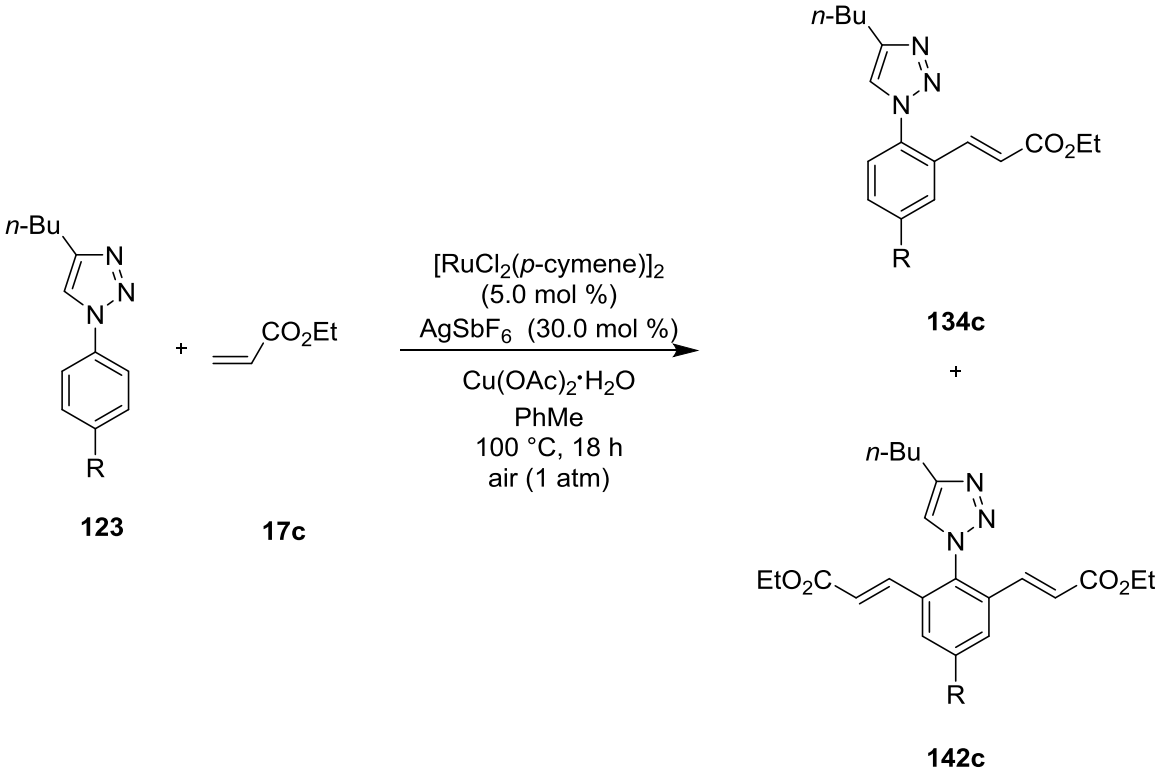
123b **17c** **134bc**

entry	oxidant	atmosphere	yield (%)
1	$Cu(OAc)_2 \cdot H_2O$	N_2	39
2	$Cu(OAc)_2 \cdot H_2O$	air	71
3	AgOAc	N_2	31
4	AgOAc	air	56
5	$Cu(OAc)_2$	N_2	22
6	Ag_2CO_3	N_2	31

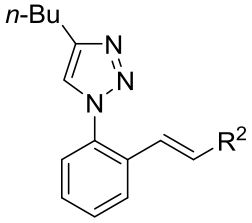
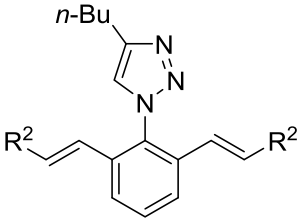
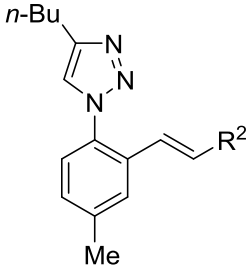
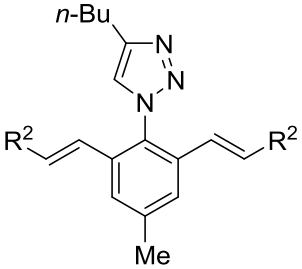
[a] General reaction conditions: **123b** (0.50 mmol), **17c** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.60 mmol), PhMe (2.0 mL), 100 °C, 18 h, yields of isolated products.

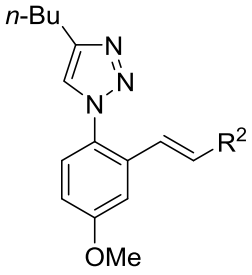
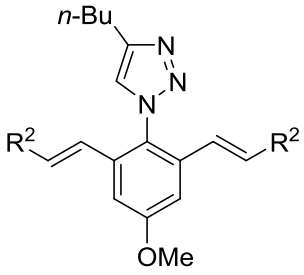
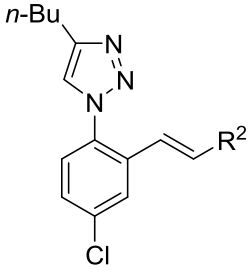
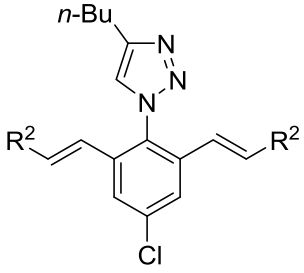
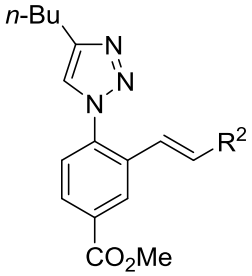
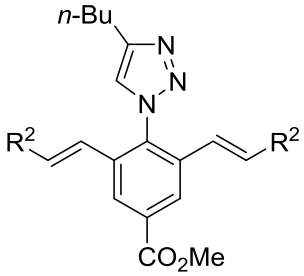
Having identified the simplified reaction conditions, which could be applied on every *N*-aryl-1,2,3-triazole **123** substrate, the results are summerized in Table 15. For substrates **123j** (*para*-chloro) and **123l** (*para*-ester) the reaction time was extended to 24 h.

Table 15: Substrate scope for the oxidative C−H alkenylations of the unsubstituted **123b** and *para*-substituted *N*-aryl-1,2,3-triazoles **123**.[a]



123 **17c** **134c** + **142c**

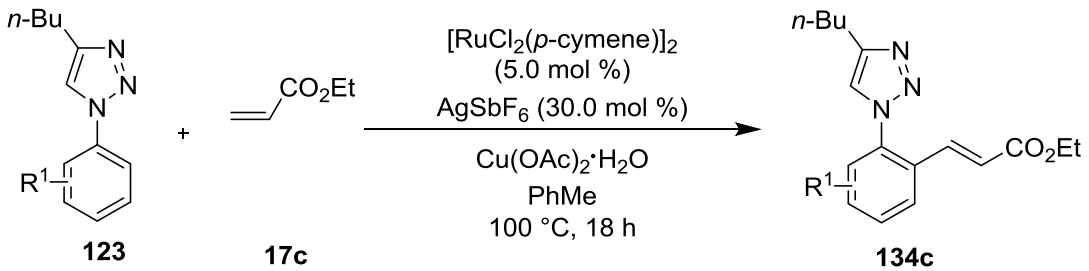
entry	substrate 123	product 134	yield [%]	product 142	yield [%]
1	R^1 = H		71		8
	123b	**134bc**		**142bc**	
2	R^1 = Me		56		12
	123i	**134ic**		**142ic**	

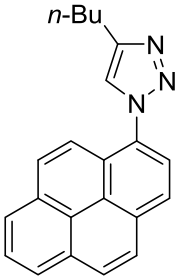
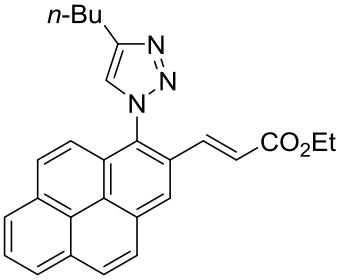
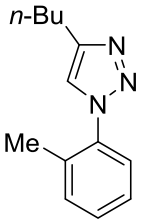
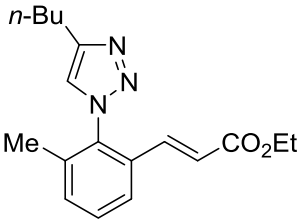
3	R^1 = OMe		75		---
	123k	**134kc**		**142kc**	
4	R^1 = Cl		53		---
	123j	**134jc**		**142jc**	
5	R^1 = CO_2Me		55		---
	123l	**134lc**		**142lc**	

[a] General reaction conditions: **123** (1.00 mmol), **17c** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.20 mmol), PhMe (4.0 mL), 100 °C, 18 h, air (1 atm), R^2 = CO_2Et, yields of isolated products.

The aerobic conditions could also successfully be applied to the standard substrate in 69% yield (Table 16, entry 2).

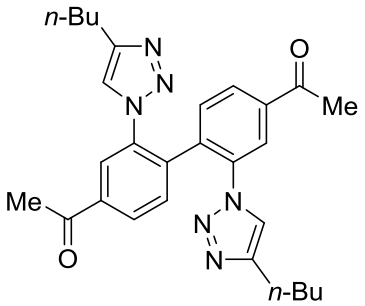
Table 16: Application of the new reaction conditions for selected *N*-aryl-1,2,3-triazoles **123**.[a]



entry	substrate 123	product 134	yield [%]
1	 **123p**	 **134pc**	28
2	 **123a**	 **134ac**	69

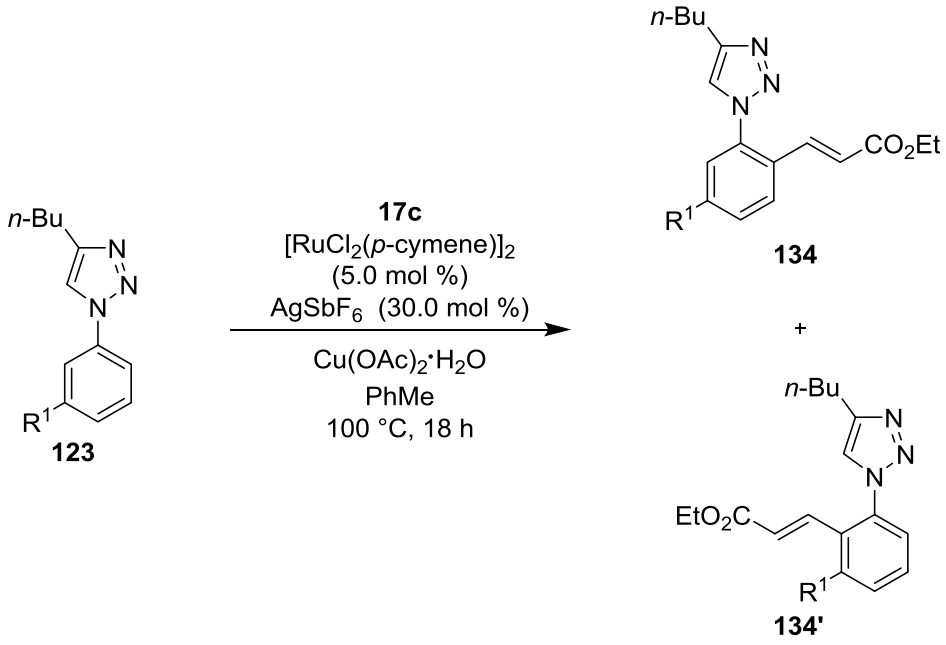
[a] General reaction conditions: **123** (0.50 mmol), **17c** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.60 mmol), PhMe (2.0 mL), 100 °C, 18 h, air (1 atm), yields of isolated products.

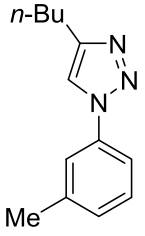
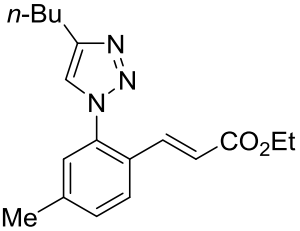
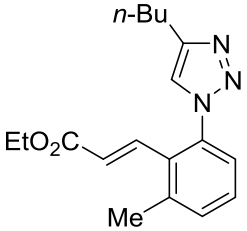
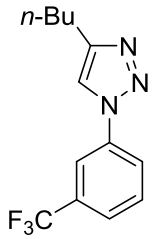
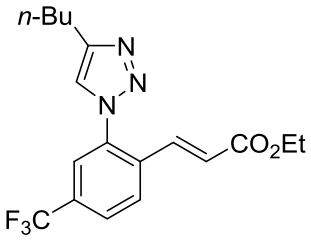
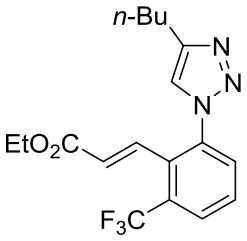
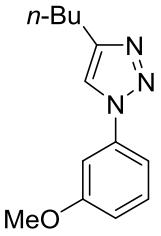
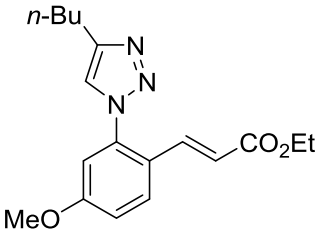
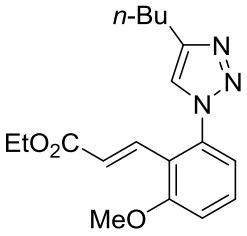
The newly developed reaction conditions also turned out to be suitable for the oxidative alkenylation of the *meta*-substituted substrates (Table 17). The *meta*-methyl **123f** and the *meta*-triflouromethyl-substituted substrates **123p** gave the desired product in satisfactory yield. Interestingly, we obtained an additional product, when using a fluoro or a methoxy group in *meta*-position, which emerged from the secondary directing effect. However, as the entry 3 illustrates, the methoxy group is not the better secondary directing group, furnishing 29% of product **134dc'**, because of the steric effect of the methoxy group, which is bulkier than the fluoro group. With a ketone in the *meta*-position the yield dropped to 17%. This was due to the oxidative dimerization of the starting material. The dimerized product could be isolated in 11% (**143**).

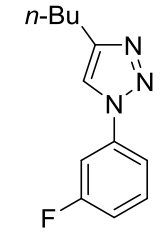
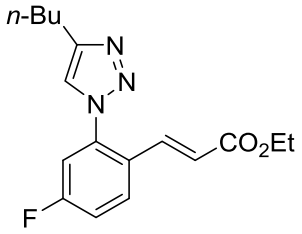
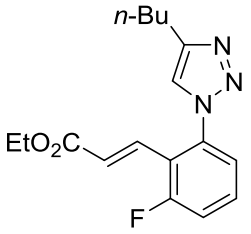
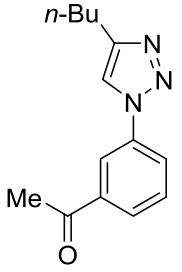
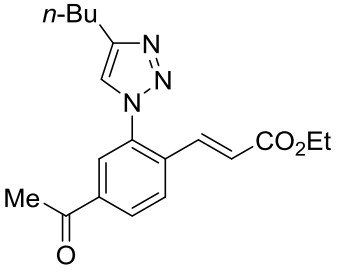
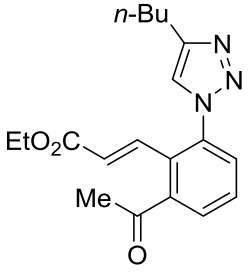


Scheme 3.4: Dimerized product **143**.

Table 17: Substrate scope for alekenylations of *meta*-substituted *N*-aryl-1,2,3-triazoles **123**.[a]

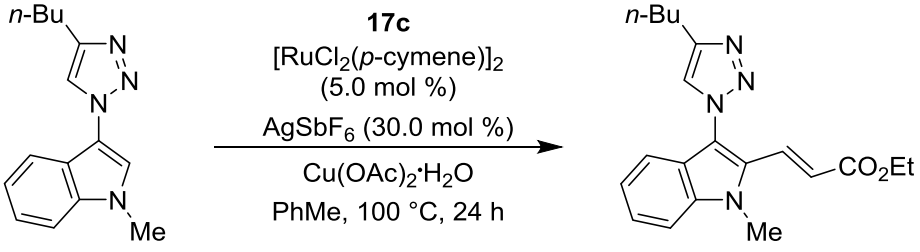


entry	substrate 123	product 134	yield [%]	product 134‘	yield [%]
1	 **123c**	 **134cc**	65	 **134cc‘**	---
2	 **123m**	 **134mc**	62	 **134mc‘**	---
3	 **123d**	 **134dc**	37	 **134dc‘**	29

4	 **123e**	 **134ec**	15	 **134ec'**	42
5	 **123n**	 **134nc**	17	 **134nc'**	---

[a] General reaction conditions: **123** (1.00 mmol), **17c** (3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.20 mmol), PhMe (4.0 mL), 100 °C, 18 h, air (1 atm), yields of isolated products.

The indole substrate **123o** also gave the alkenylated product **134oc** in a site selective fashion (Scheme 3.5).



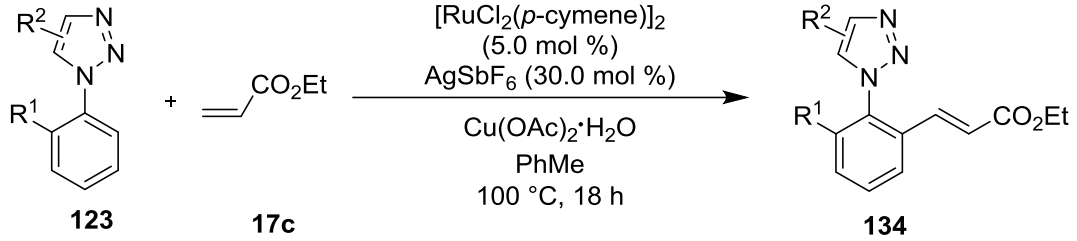
123o **134oc**: 50%

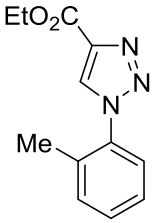
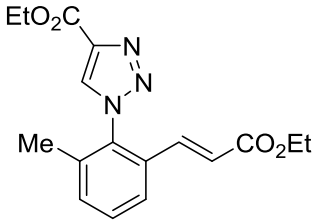
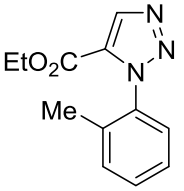
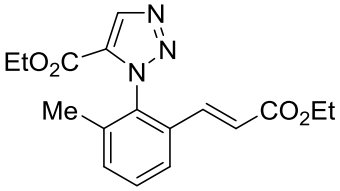
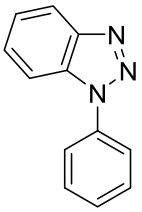
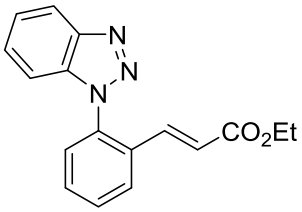
Scheme **3.5**: Oxidative C−H alkenylation of 3-(4-butyl-1*H*-1,2,3-triazol-1-yl)-1-methyl-1*H*-indole **123o**.

So far, we focused on the influence of different substituents on the aromatic moiety. Next, we investigated the reactivity of different substitution patterns of the triazole directing group (Table 18).

The electron-withdrawing ester group on the triazole decreased the reactivity in the C−H bond functionalization reaction. When the ester-substituent is on the 4 position the yield was relatively low, while the ester-substituent in the 5 position of the triazole shut down the reaction. This is because the sterical effect of the ester group inhibited the alkenylation on the aryl moiety. Furthermore the ester is decreasing the electron-density of the triazole, and thereby its directing group power. A benzo[d][1,2,3]triazole as directing group also decreased the amount of alkenylated product (entry 3).

Table 18: Substrate scope of alkenylations with respect to substitution of the triazole directing group.[a]



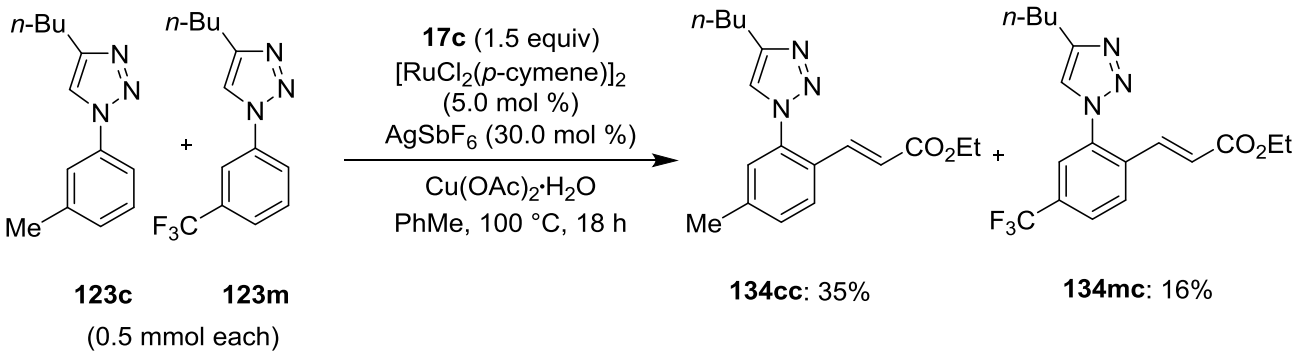
entry	substrate 123	product 134	yield [%]
1	 **123q**	 **134qc**	38
2	 **123r**	 **134rc**	---
3	 **123s**	 **134sc**	20

[a] General reaction conditions: **123** (0.50 mmol), **17c** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (30.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.60 mmol), PhMe (2.0 mL), 100 °C, 18 h, air (1 atm), yields of isolated products.

3.3.3 Mechanistic Studies

3.3.3.1 Intermolecular Competition Experiment

Given the high catalytic efficacy of the optimized catalyst, we became intrigued by probing its mode of action. The competition experiment between the *meta*-substituted trifluoromethyl-substituted substrate **123m** and the methyl-substituted substrate **123c** revealed that electron-rich substrates are preferred for this alkenylation reaction (Scheme 3.6). This reactivity pattern is in accordance with an electrophilic-type activation manifold.



123c **123m**
(0.5 mmol each)

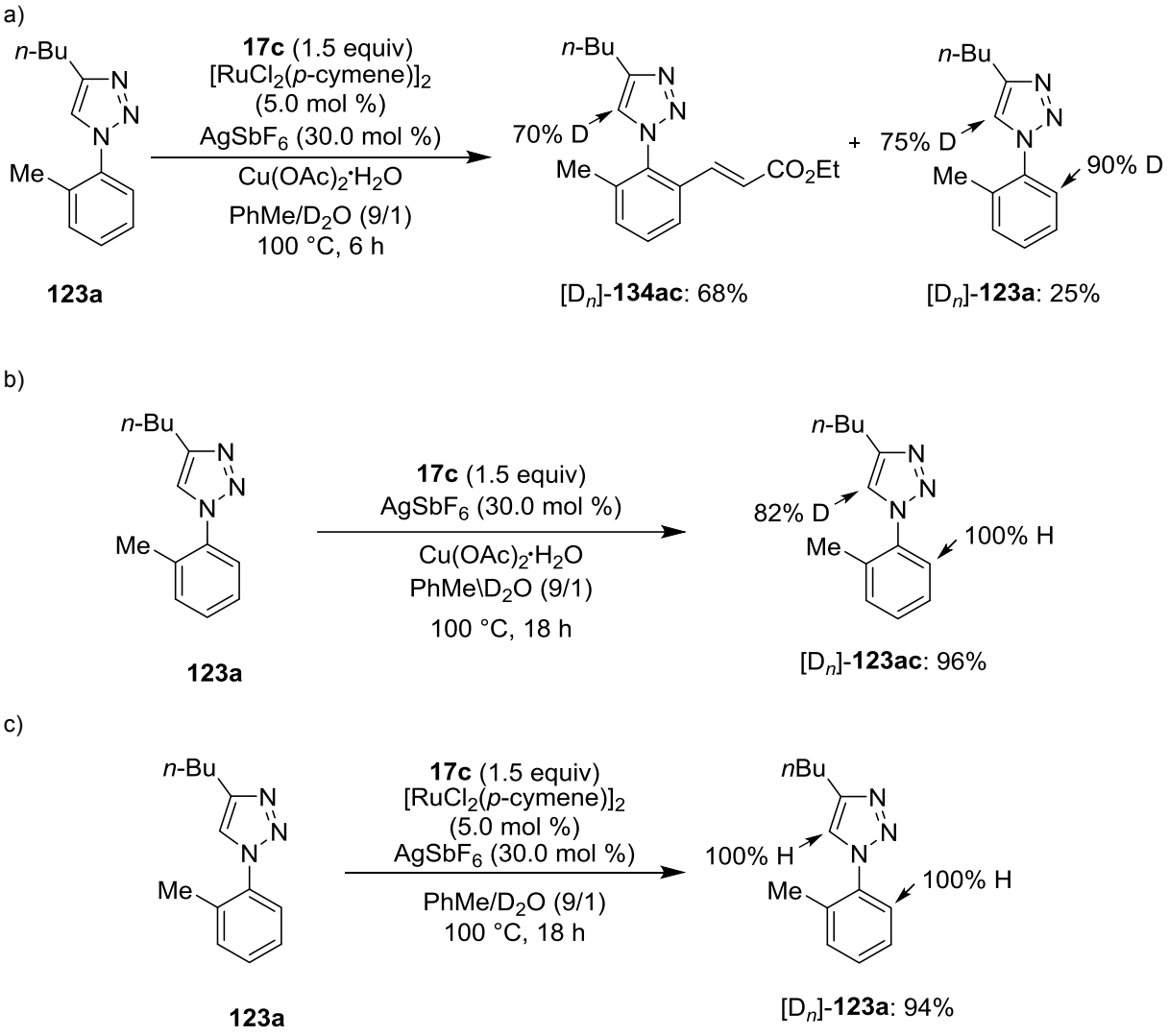
134cc: 35% **134mc**: 16%

Scheme 3.6: Intermolecular competition experiment with triazoles **123c** and **123m**.

3.3.3.2 Ruthenium-Catalyzed H/D Exchange Experiment

Further support for this mechanistic rationale was obtained from oxidative alkenylations in the presence of D_2O as a cosolvent, which indicates a significant H/D scrambling in the *ortho*-position of the reisolated substrate [D_n]-**123a**. The experiment also showed an H/D-exchange of the proton in position 5 of the *N*-aryl-1,2,3-1*H*-triazole, which is due to the activation by the $Cu(OAc)_2 \cdot H_2O$ already known in literature (Scheme 3.7 a & 3.7 b).[104] Without $Cu(OAc)_2 \cdot H_2O$ there is no H/D exchange in the substrate **134a** (Scheme 3.7 c), underlining the importance of the ruthenium(II) carboxylate complex.

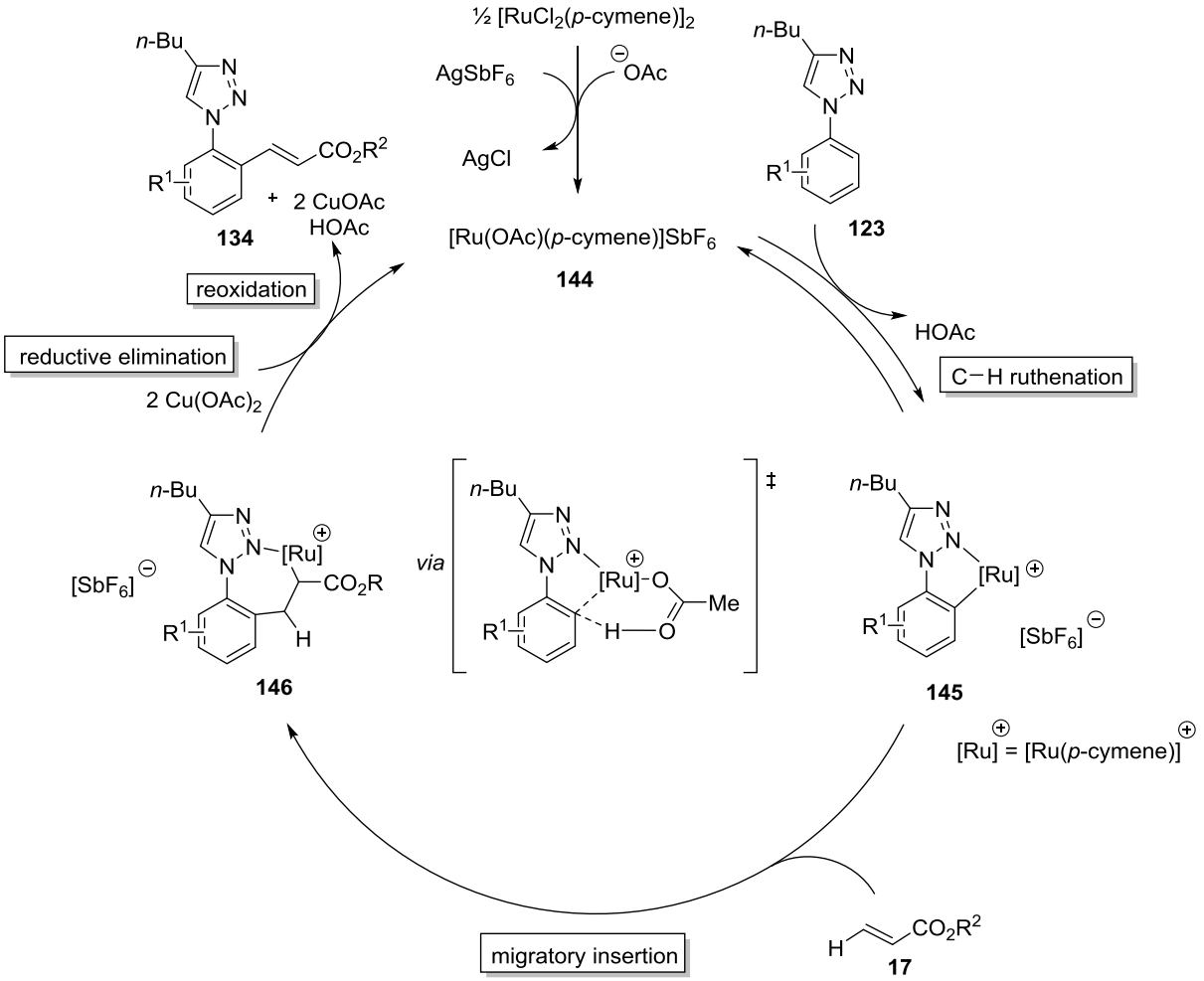
[104] L. Ackermann, H. K. Potukuchi, *Org. Biomol. Chem.* **2010**, *8*, 4503−4513.



Scheme 3.7: Oxidative alkenylations in the presence of D_2O.

3.3.3.3 Proposed Catalytic Cycle

Based on these mechanistic studies, we propose the C−H bond activation to occur by a reversible electrophilic-type metalation event (Scheme 3.8), which in turn explains the unique activity of the *in-situ* formed cationic ruthenium(II) complex. The thus-formed cycloruthenated complex **145** subsequently undergoes a migratory insertion with the alkene **17** to furnish the intermediate **146**. Finally, *β*-hydride elimination yields the desired product **134**. Oxidation of the catalyst by $Cu(OAc)_2{\cdot}H_2O$ regenerates the catalytically active ruthenium complex.



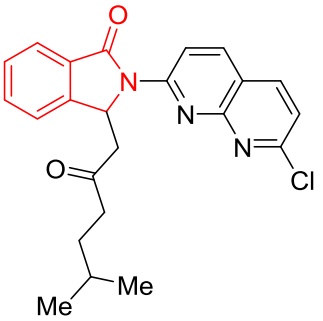
Scheme 3.8: Proposed catalytic cycle.

In conclusion, we have developed the ruthenium(II)-catalyzed direct oxidative alkenylation of *N*-aryl-1,2,3-triazoles **123**. The high catalytic capability and robustness of the cationic ruthenium(II) complex was underlined by employing aerobic reaction conditions. The ruthenium-catalyzed C−H bond functionalization proceeded with excellent chemo-, site- and diastereo-selectivities, based on the reversible formation of the five-membered ruthenacycles as the key intermediate. This successfully completed alkenylation project of the *N*-aryl-1,2,3-triazoles and their close connection to the pharmaceutical application, led us to our next project; the synthesis of valuable isoindolinones *via* direct C−H/N−H bond functionalization.

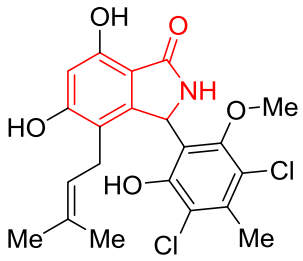
3.4 Annulation of Acrylates through Ruthenium(II)-Catalyzed Direct C−H/N−H Bond Functionalization of *N*-Tosylbenzamides

The recent years have witnessed some developments in the metal-catalyzed synthesis of isoindolinones, for instance by *Falck* and *Zhu*,[105] avoiding the multiple step synthesis of the core structure, using relatively expensive palladium or rhodium catalysts for the C−H bond functionalization.

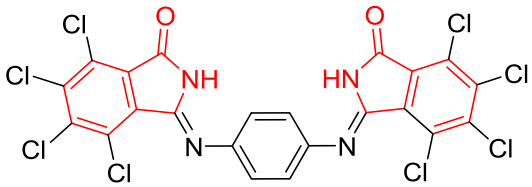
These new developments and extensive studies on the synthesis of these substrates are due to their widespread application. For example, pagoclone, has been commercialized as an anxiolytic drug (Scheme 3.9).[106] Pestalachloride A is an inhibitor for the therapeutic intervention in cancer cells (Scheme 3.9).[107] Another wide area of the application of isoindolinones is centered on coloring pigments in lacquers and varnish industry, with an example being the pigment yellow 110 (Scheme 3.9).[108]



Pagoclone



Pestalachloride A



pigment yellow 110

Scheme 3.9: Apllied isoindolinone derivatives.

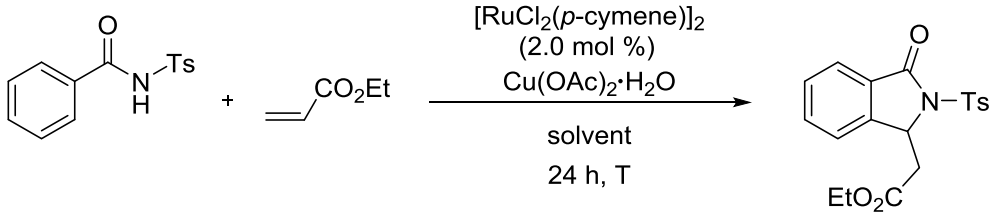
[105] a) C. Zhu and J. R. Falck, *Org. Lett.* **2011**, *13*, 1214−1217; b) C. Zhu and J. R. Falck, *Chem. Comm.* **2011**, *13*, 1214−1217.
[106] T. L. Stuk, B. K. Assink, R. C. Bates, J. D. T. Erdman, V. Fedij, S. M. Jennings, J. A. Lassig, R. J. Smith, T. L. Smith, *Organic Process Research & Development*, **2003**, *7*, 851−855.
[107] N. Slavov, J. Cvengros, J.-M. Neudörfl, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2010**, *49*, 7588−7591.
[108] IN 250748| Isoindolinone pigments and a method of manufacturing|5 Febuary 2007|S. Racherla, C. R. Shashidhur, R. Chitale, D. B. Bajirao.

In this project, we focused on the ruthenium(II)-catalyzed annulation reaction of the cheap and easily accessible *N*-tosylbenzamides **135** with acrylates **17** resulting in the synthesis of isoindolinones.

3.4.1 Optimization Studies for the Annulation of Acrylates through Ruthenium(II)-Catalyzed Direct C−H/N−H Bond Functionalization of *N*-Tosylbenzamides

We started our screening with different solvents and different reaction temperatures using the standard conditions for the oxidative direct alkenylation reactions (Table 19). Good results were obtained in water at 100 °C (Table 19, entry 5) or in methanol at 65 °C (Table 19, entry 14). Other solvents did not give the desired product in acceptable amounts. In the case of DCE the addition of catalytic amounts of silver hexafluoroantimonate to the reaction mixture increased the product yield dramatically, but still remained far beyond the yields obtained in methanol or water.

Table 19: Optimization studies for the annulation of *N*-tosylbenzamides **135** with ethylacrylate **17c**.[a]



135a **17c** **136ac**

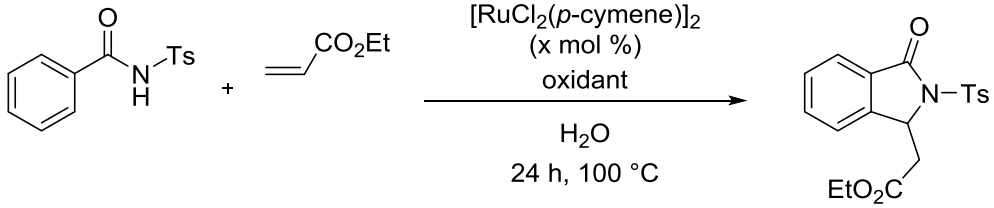
entry	solvent	T [°C]	yield [%]
1	PhMe	130	23
2	AcOH	120	7
3	PhMe	100	28
4	PhCl	100	14
5	H_2O	100	48
6	*t*-AmOH	100	15
7	DMF	100	10
8	DMSO	100	17
9	1,4-dioxane	100	---
10	MeCN	82	trace
11	DCE	82	---

12	DCE	82	43[b]
13	DCE	82	---[c]
14	MeOH	65	56

[a] General reaction conditions: **135a** (1.00 mmol), **17c** (1.20 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.10 mmol), solvent (5.0 mL), T, 24 h, yields of isolated products; [b] $AgSbF_6$ (30.0 mol %); [c] KPF_6 (30.0 mol %).

Next, oxidants other than $Cu(OAc)_2 \cdot H_2O$ were examined, as well as various catalyst loadings (Table 20) formed to improve the amount of product. Changing the oxidant to silver acetate or using a mixture of copper bromide and sodium acetate,[75a] decreased the yield significantly (Table 20, entry 3). Without the catalyst there was no conversion (entry 4). Increasing the catalyst loading to 5.0 mol % only led to a slight increase in the yield (Table 20, entry 5). To our delight, when lowering the amount of catalyst to 1.0 mol % the yield remained the same as before (Table 20, entry 6). The reduction of the amount of the acrylate to 1.05 equiv had no effect on the isolated yield (Table 20, entry 7). Furthermore, the reaction was found to be feasible under air (Table 20, entry 8). Reducing the reaction time to 16 h and reducing the reaction temperature to 65 °C led to lower amount of the desired product (Table 20, entry 9 and 10).

Table 20: Optimization studies for the annulation of *N*-tosylbenzamides with acrylate: Oxidant and catalyst loading.[a]



135a **17c** **136ac**

entry	oxidant	$[RuCl_2(p\text{-cymene})]_2$ [mol %]	yield [%]
1	$Cu(OAc)_2 \cdot H_2O$	2	48
2	AgOAc	2	30
3	$CuBr_2$ (NaOAc, 3.0 equiv)	2	---
4	$Cu(OAc)_2 \cdot H_2O$	-	---
5	$Cu(OAc)_2 \cdot H_2O$	5	54
6	$Cu(OAc)_2 \cdot H_2O$	1	49
7	$Cu(OAc)_2 \cdot H_2O$	1	52[b]
8	$Cu(OAc)_2 \cdot H_2O$	1	52[b,c]
9	$Cu(OAc)_2 \cdot H_2O$	2	38[d]

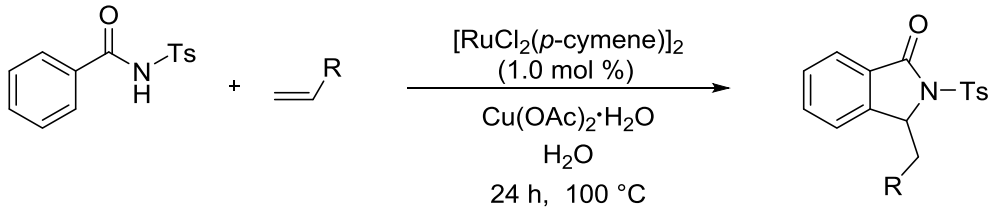
10	$Cu(OAc)_2 \cdot H_2O$	1	44[e]

[a] General reaction conditions: **135a** (1.00 mmol), **17c** (1.20 mmol), $[RuCl_2(p\text{-cymene})]_2$ (x mol %), oxidant (2.10 mmol), solvent (5.0 mL), T, 24 h, yields of isolated products; [b] **17c** (1.05 mmol); [c] air (1 atm); [d] 16 h; [e] 65 °C.

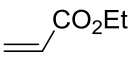
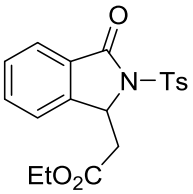
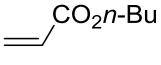
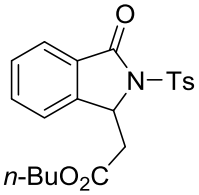
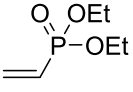
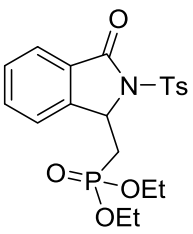
3.4.2 Scope and Limitations for the Direct C−H/N−H Bond Functionalization of *N*-Tosylbenzamides with Acrylates

With the optimized reaction conditions in hand, we extended the substrate scope and therefore different alkenes were explored (Table 21). While ethyl acrylate **17c** gave the highest yield, the yields of the other acrylates were comparable. Even with the diethyl vinylphosphonate the yield was moderate.

Table 21: Substrate scope for alkenylations of *N*-tosylbenzamide **135** with different alkenes **17**.[a]



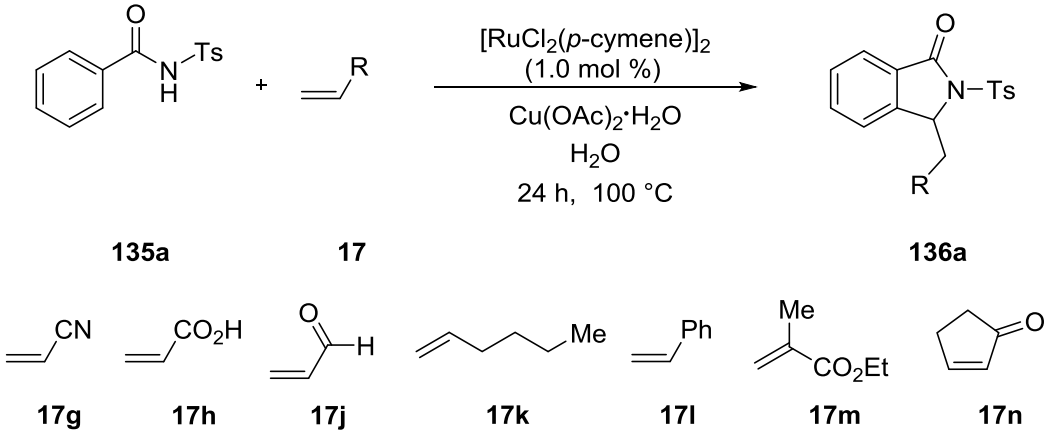
154a **17** **136a**

entry	alkene 17	product 136	yield [%]
1			52
	17c	**136ac**	
2			47
	17e	**136ae**	
3			44

	17k	**136ak**

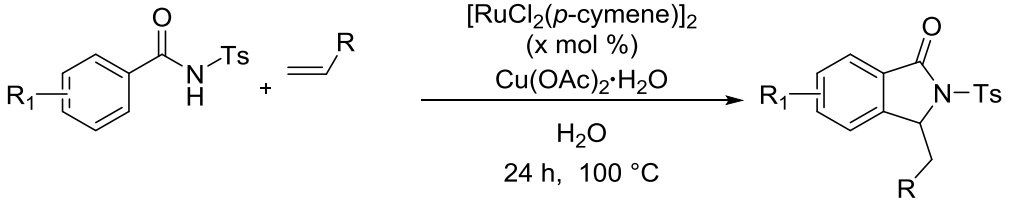
[a] General reaction conditions: **135a** (1.00 mmol), **17** (1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.10 mmol), H_2O (5.0 mL), 100 °C, 24 h, yields of isolated products.

The following challenging alkenes (Scheme 3.10) acrylonitrile, acrylic acid or acrolein **17g-17j** did not give the desired product. Furthermore, no product could be obtained using unactivated alkene 1-hexene **17k** or styrene **17l**. The disubstituted alkenes ethyl methacrylate **17m** and cyclopentenone **17n** were found to be unreactive as well under otherwise identical reaction conditions.

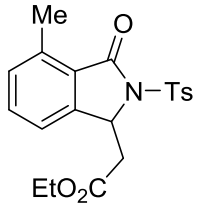


Scheme 3.10: Alkenes which did not react.

To probe the influence of the catalyst loading with different substrates **135**, we examined annulations with several substrates **135b und 135c** at different catalyst loadings (Scheme 3.11). Satisfactorily, we observed good yields even with 1.0 mol % of the catalyst, which could be improved by using higher catalyst loadings. The yield ranged from moderate to very good.

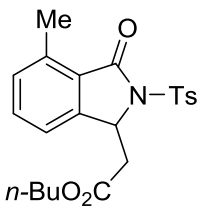


135 **17** **136**



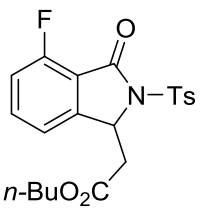
136bc

52% (1.0 mol % cat.)
64% (2.0 mol % cat.)
74% (5.0 mol % cat.)



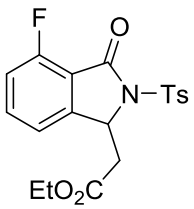
136be

45% (1.0 mol % cat.)
67% (2.0 mol % cat.)
88% (5.0 mol % cat.)



136cc

59% (1.0 mol % cat.)
68% (2.5 mol % cat.)
78% (3.0 mol % cat.)



136cc

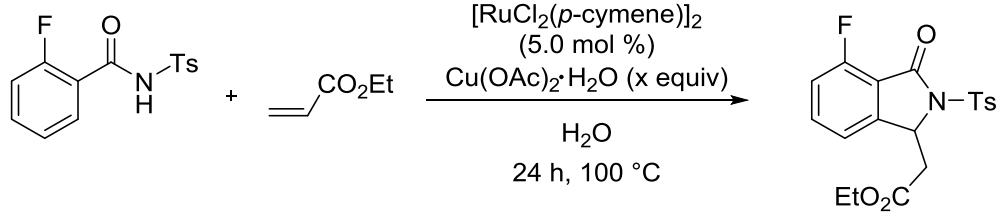
59% (1.0 mol % cat.)
71% (2.5 mol % cat.)
78% (5.0 mol % cat.)

Scheme 3.11: Influence of the catalyst loading on the reaction with different substratets.[a]

[a] General reaction conditions: **135** (1.00 mmol), **17** (1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (x mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.10 mmol), H_2O (5.0 mL), 100 °C, 24 h, yields of isolated products.

In order to explore whether stoichiometric amounts of copper acetate are needed for this reaction, we examined the reaction of 2-fluoro-*N*-tosylbenzamide **135c** with different quantities of $Cu(OAc)_2{\cdot}H_2O$. The yield was dependent on the amount of the $Cu(OAc)_2{\cdot}H_2O$ (Table 22), and 1.5 equivalents were found to be optimal.

Table 22: Influence of the amount of $Cu(OAc)_2{\cdot}H_2O$.[a]



135c **17c** **136cc**

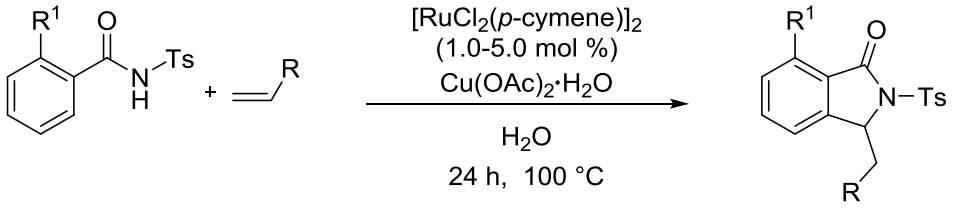
entry	$Cu(OAc)_2{\cdot}H_2O$	yield [%]
1	0.3	38
2	0.5	50
3	1	57
4	1.2	67

5	1.5	67
6	2.1	66

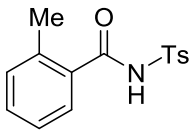
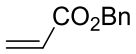
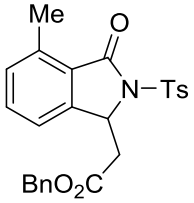
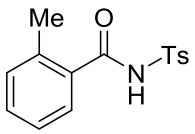
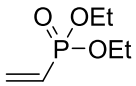
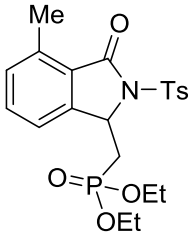
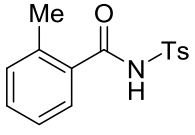
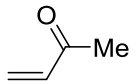
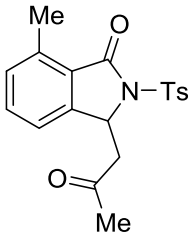
[a] General reaction conditions: **154c** (1.00 mmol), **17c** (1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$, H_2O (5.0 mL), 100 °C, 24 h, yields of isolated products.

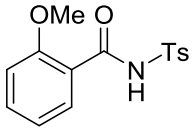
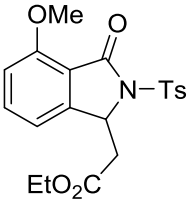
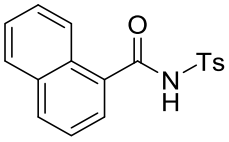
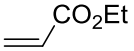
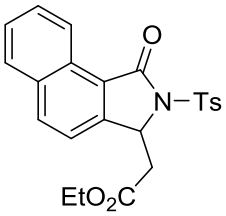
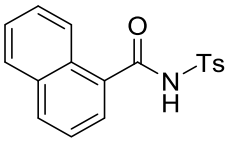
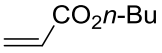
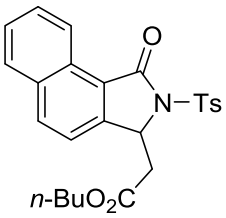
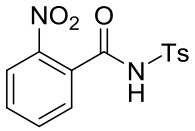
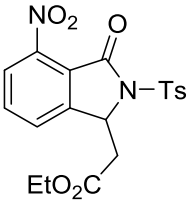
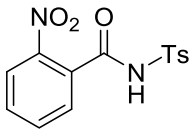
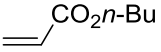
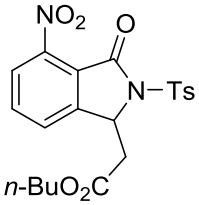
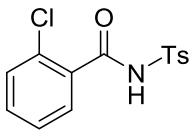
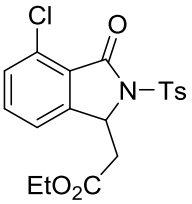
Next, the substrate scope of the alkenylation was examined in detail. The *ortho*-methyl-substituted substrate **135b** was very reactive, but with the diethyl vinylphosphonate **17k** and the methylvinylketone **17j** the yield dropped significantly. When using the *ortho*-methoxy-substituted *N*-tosylbenzamide the yield was only moderate, even with 5.0 mol % catalyst loading (Table 23, entry 4). Other functional groups, such as chloro or nitro groups, were well tolerated and afforded the desired product in good yields.

Table 23: Substrate scope for alkenylations of *ortho*-substituted *N*-tosylbenzamides **135**.[a]



135 **17** **136**

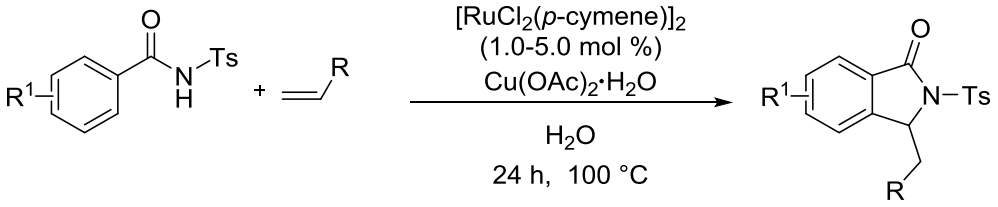
entry	substrate 135	alkene 17	product 136	yield [%]
1				82
	135b	**17d**	**136bd**	
2				48
	135b	**17k**	**136bk**	
3				25[b]

	135b	**17j**	**136bj**	
4				52
	135d	**17c**	**136dc**	
5				68
	135e	**17c**	**136ec**	
6				58
	135e	**17e**	**136ee**	
7				59
	135f	**17c**	**136fc**	
8				59
	135f	**17c**	**136fe**	
9				60
	135g	**17c**	**136gc**	

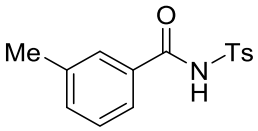
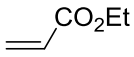
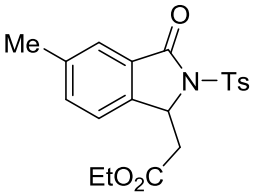
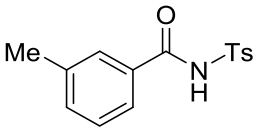
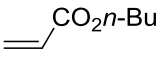
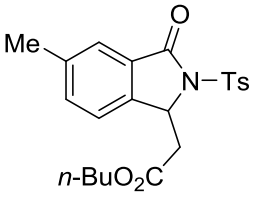
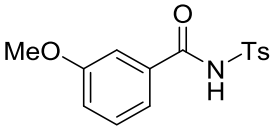
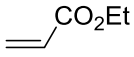
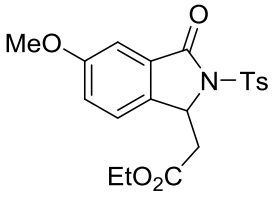
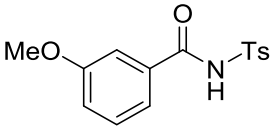
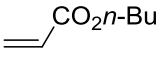
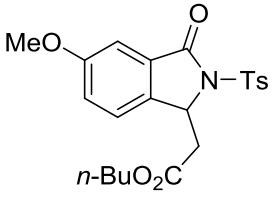
[a] General reaction conditions: **135a** (1.00 mmol), **17** (1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.10 mmol), H_2O (5.0 mL), 100 °C, 24 h, yields of isolated products; [b] $[RuCl_2(p\text{-cymene})]_2$ (1.0 mol %).

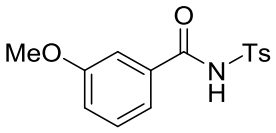
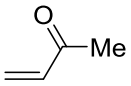
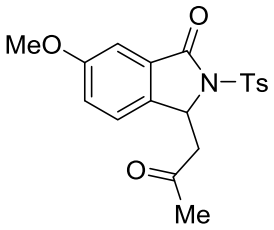
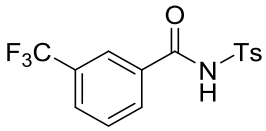
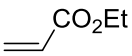
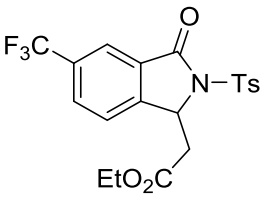
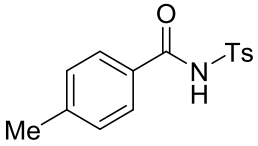
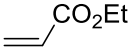
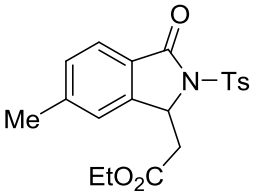
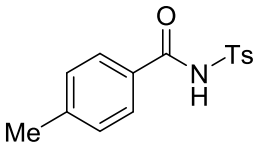
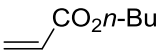
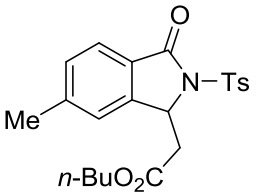
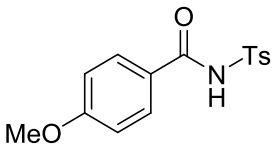
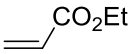
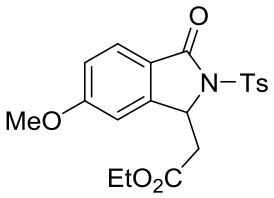
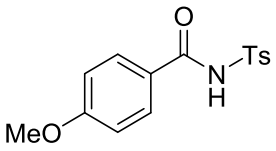
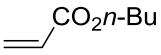
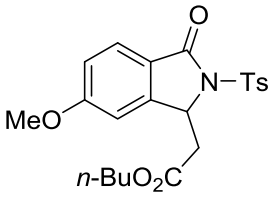
Meta- and *para*-substituted substrates worked well, regardless of the substitution with the methyl-, the methoxy- (Table 24, entries 1-5) or the fluoro-group.

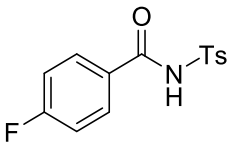
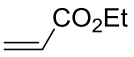
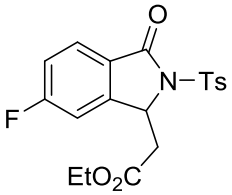
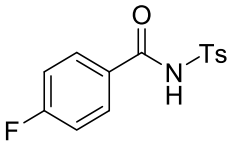
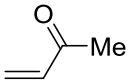
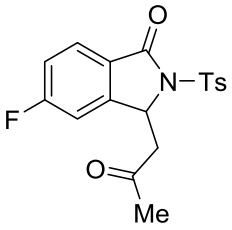
Table 24: Substrate scope for alkenylations of *meta*- and *para*-substituted *N*-tosylbenzamides **135**.[a]



135 **17** **136**

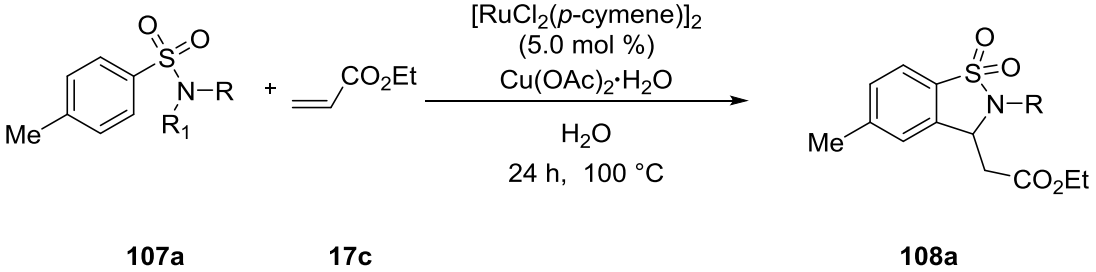
entry	substrate 135	alkene 17	product 136	yield [%]
1				63[b]
	135h	**17c**	**136hc**	
2				60[b]
	135h	**17e**	**136he**	
3				51
	135i	**17c**	**136ic**	
4				61
	135i	**17e**	**136ie**	

5				27 [b]
	135i	**17j**	**136ij**	
6				78
	135j	**17c**	**136jc**	
7				52[b]
	135k	**17c**	**136kc**	
8				50[b]
	135k	**17e**	**136ke**	
9				52
	135l	**17c**	**136lc**	
10				52
	135l	**17e**	**136le**	

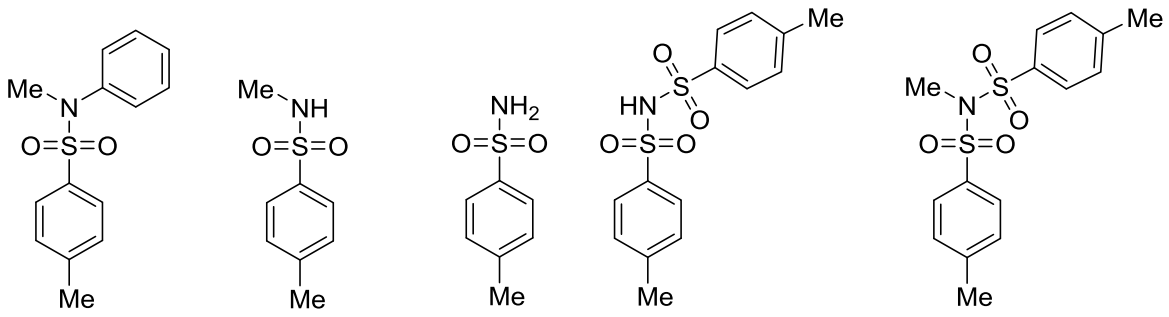
11				49
	135m	**17c**	**136mc**	
12				58
	135m	**17j**	**136mj**	

[a] General reaction conditions: **135** (1.00 mmol), **17** (1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.10 mmol), H_2O (5.0 mL), 100 °C, 24 h, yields of isolated products; [b] $[RuCl_2(p\text{-cymene})]_2$ (1.0 mol %).

Despite the broad applicability of the reaction on various *N*-tosylbenzamides, there are some limitations. Blocking the nitrogen, which is coordinating to the ruthenium complex, with a methyl group, shuts down the reaction. Further, we did not observe the competitive alkenylation on the sulfonamide moiety. Even using several other substrates, no sulfonamide-directed alkenylation reaction was observed (Scheme 3.12).



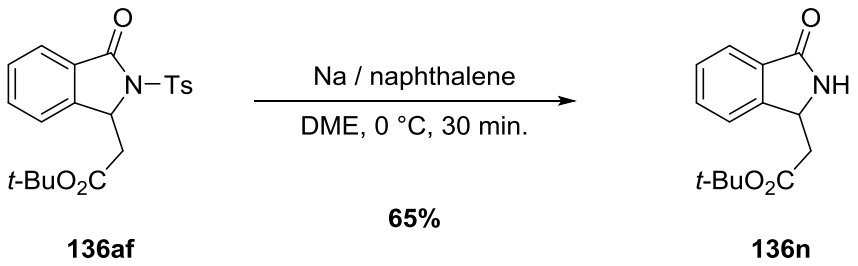
107a **17c** **108a**



107b **107c** **107d** **107e** **107f**

Scheme 3.12: Limitations in the synthesis of sultams **108**.

The *N*-tosyl group of the isoindolinone can be easily cleaved by a known procedure, giving the free isoindolinone **136n** (Scheme 3.13).[105]



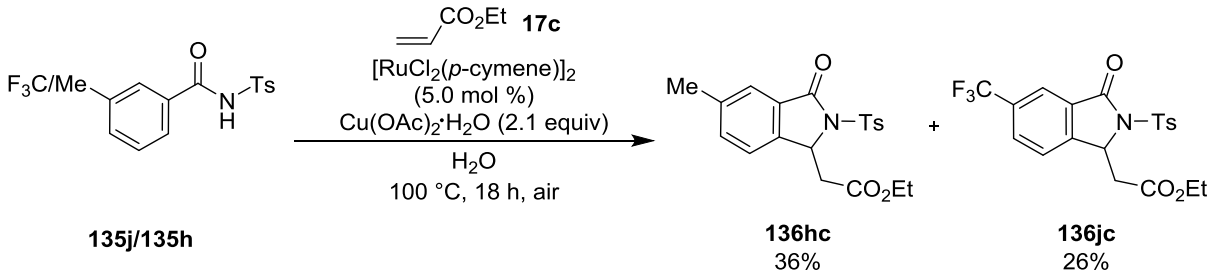
136af **136n**

Scheme 3.13: Cleavage of the tosyl group

3.4.3 Mechanistic Studies

3.4.3.1 Intermolecular Competition Experiment

To gain insight into the mechanistic course of the ruthenium-catalyzed oxidative annulation of alkenes **17** with *N*-tosylbenzamides **135** *via* C–H/N–H bond cleavages, an intermolecular competition experiment was performed (Scheme 3.14). The competition experiment between the *meta*-substituted substrates **135j** and **135h** revealed that electron-rich substrates are preferred for this cyclization reaction.



135j/135h

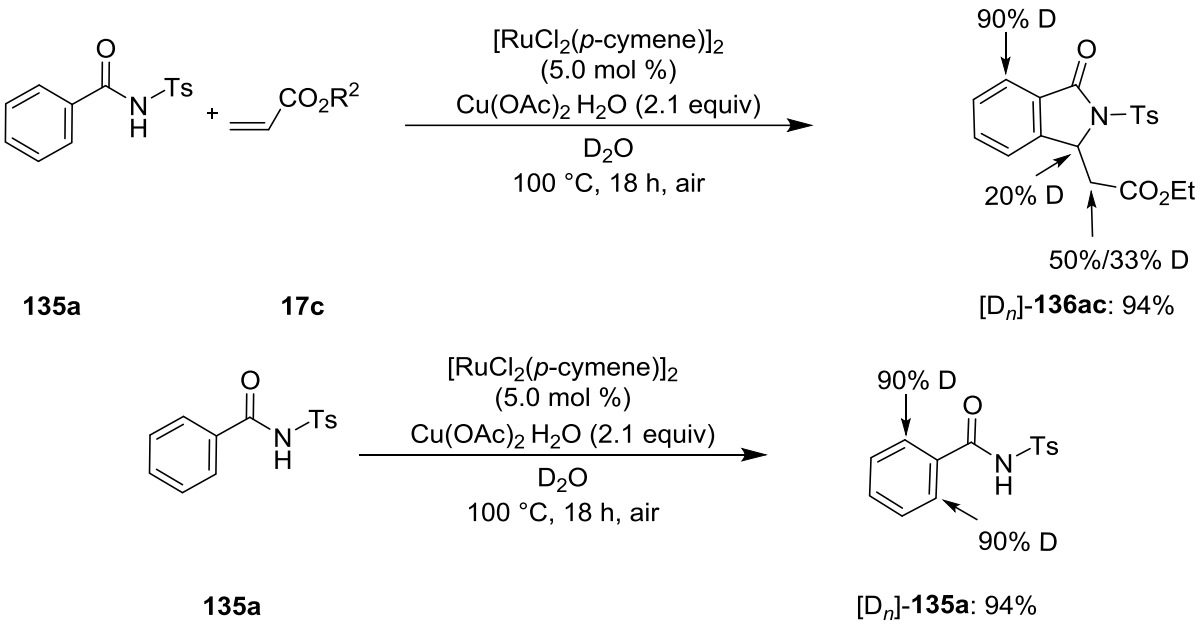
136hc 36%

136jc 26%

Scheme 3.14: Intermolecular competition experiment with *N*-tosylbenzamides **135j** and **135h**.

3.4.3.2 H/D Exchange Experiments

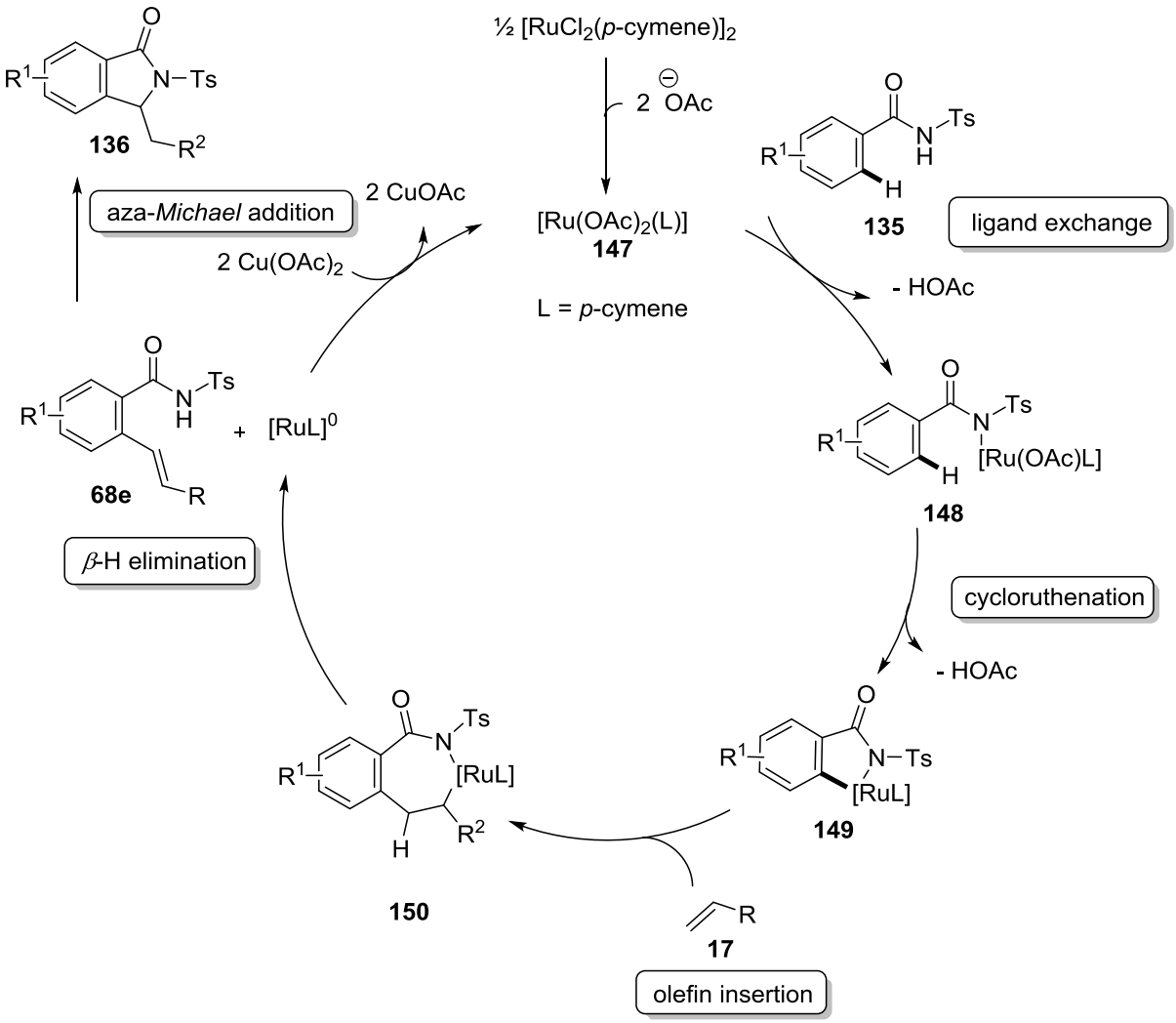
Mechanistic studies on the oxidative alkenylation in the presence of D_2O were performed. Scheme 3.15 presents the result of the H/D-exchange. In the *ortho*-positions of the reisolated *N*-tosylbenzamide [D_n]-**135c** as well as of the product [D_n]-**136**, we observed a significant H/D scrambling, which revealed the reversible nature of the C−H ruthenation step. Further H/D-exchange of the inserted alkene is strong evidence for an aza-*Michael* reaction (Scheme 3.15).



Scheme 3.15: Oxidative alkenylation in the presence of D_2O.

3.4.3.3 Proposed Catalytic Cycle

Based on these mechanistic studies, we propose the C−H bond activation to involve a reversible electrophilic-type metalation event (Scheme 3.16) with a ruthenium(II) complex forming **147**. Subsequently, this intermediate undergoes migratory insertion with the alkene **17**. The intermediate **149** undergoes reductive elimination, to yield the alkenylated *N*-tosylbenzamide. Afterwards the nucleophilic cyclization resulted in the desired isoindolinone **136**. Oxidation by $Cu(OAc)_2$ regenerates the catalytically active ruthenium complex.

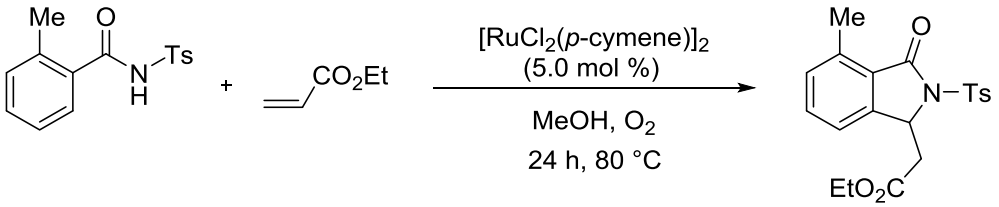


Scheme 3.16: Propsed catalytic cycle.

In summary, we have developed the unpredented ruthenium(II)-catalyzed oxidative alkenylation/annulation of arenes through C−H/N−H bond functionalization. This led us to the final project of this thesis, the oxidative alkenylation of *N*-tosylbenzamides with oxygen as the terminal oxidant and water as the sole by-product.

3.5 Annulation of Acrylates through Ruthenium(II)-Catalyzed Direct C−H/N−H Bond Functionalization of *N*-Tosylbenzamides with Oxygen as Oxidant

Thus far all ruthenium(II)-catalyzed alkenylations and alkene annulations proceeded only in the presence of additional oxidants, such as copper(II) or silver(I) salts, leading to the formation of undesired stoichiometric metal containing by-products. However, some developments on the metal-catalyzed C−H bond functionalization with oxygen as the sacrificial oxidant has been made recently,[53, 55a-b, 55d-e, 58, 95] the ruthenium-catalyzed annulation with alkenes and oxygen as sole oxidant, as of yet has proven elusive. Recently, our research group developed the first ruthenium(II)-catalyzed C−H bond activation/alkyne annulation by benzoic acids under ambient oxygen atmosphere.[59] Inspired by these conditions, we adjusted the reaction temperature for the *N*-tosylbenzamide **135**. Unfortunately, the amount of the desired product was rather low, but indicated the possibility of an aerobic C−H functionalization (Scheme 3.17).



135b **17c** **136bc**

Scheme 3.17: Aerobic ruthenium(II)-catalyzed annulation of ethyl acrylate **17c**.

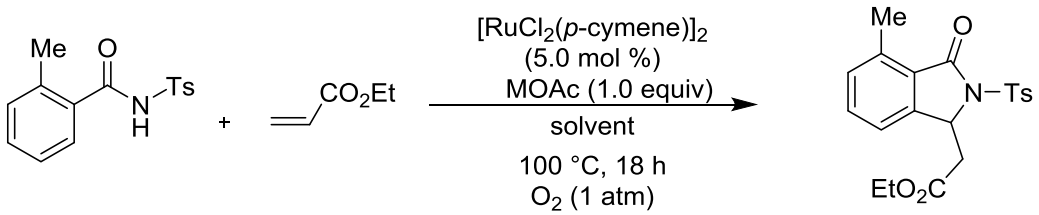
Herein we present the first ruthenium(II)-catalyzed aerobic alkene annulation of *N*-tosylbenzamides with alkenes leading to biologically active isoindolinones.

3.5.1 Optimization Studies for the Annulation of Acrylates through Ruthenium(II)-Catalyzed Direct C−H/N−H Bond Functionalization of *N*-Tosylbenzamides with Oxygen as Oxidant

At the outset of our studies we probed reaction conditions for the oxidative alkene annulation of *N*-tosylbenzamides **153b** with ethyl acrylate **17c** under an atmosphere of oxygen (Table 25). Using DMF instead of methanol decreased the isolated yield of the product **136b**. Rising the reaction temperature in DMF to 100 °C −which was not possible for methanol−, increased the yield slightly (Table 25, entry 3 and 4).

Interestingly, the best reaction conditions were without solvents (Table 25, entry 5 and 6) using a slight excess of ethyl acrylate, which was found by Keshav Raghuvanshi. Testing the different acetates in DMF or under neat reaction conditions revealed that KOAc gave better conversions than CsOAc or NaOAc. Importantly, the C−H bond functionalization did not occur in the absence of the ruthenium(II)-catalyst or the acetate (Table 25, entry 9 and 10).

Table 25: Optimization studies for the annulation of *N*-tosylbenzamides with acrylates.[a]



135b **17c** **136bc**

entry	solvent	MOAc	T [°C]	yield
1	MeOH	CsOAc	80	30
2	DMF	CsOAc	80	20
3	DMF	CsOAc	100	26
4	DMF	KOAc	100	35
5	-	CsOAc	100	68[b]
6	-	KOAc	100	86[b]
7	-	NaOAc	100	70[b]
8	-	CsOAc	100	45[b,c]
9	-	CsOAc	100	---[d]
10	-	-	100	---

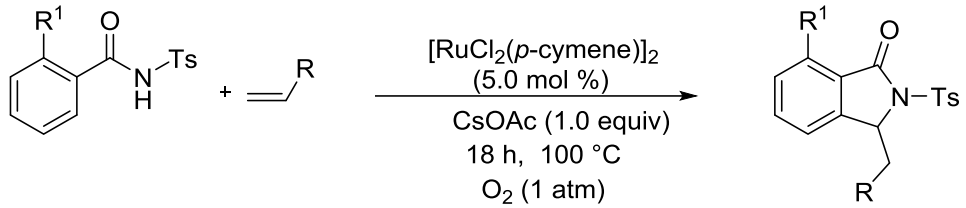
[a] Reactions conditions: **135b** (0.50 mmol), **17c** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), MOAc (1.0 equiv), solvent (2.0 mL), 100 °C, 18 h, O_2 (1 atm), yield of isolated product; [b] **17c** (2.50 mmol), without solvent; [c] with $[Ru(O_2CMes)_2p\text{-cymene}]$ **140** (5.0 mol %); [d] without $[RuCl_2(p\text{-cymene})]_2$.

3.5.2 Scope of the Aerobic Annulation of Acrylates through Ruthenium(II)-Catalyzed Direct C−H/N−H Functionalization of *N*-Tosylbenzamides

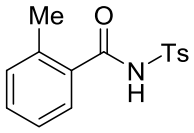
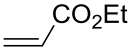
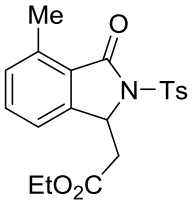
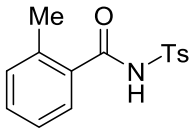
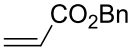
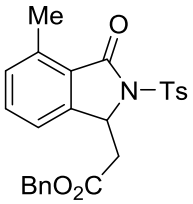
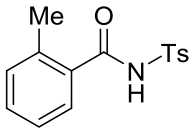
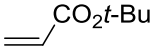
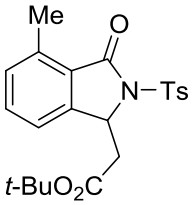
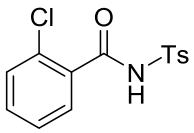
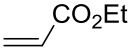
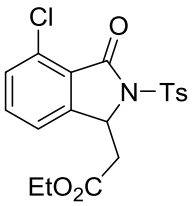
To compare the reactivity of cesium and potassium acetate, we tested their reactivity in the annulation with different *N*-tosylbenzamides **135** (Table 26). Hence the yields of the desired products were comparable. Table 26 also shows that sterically more demanding acrylates

were less reactive. Furthermore, sterically hindered substrates **135g** with *ortho*-substitution gave lower yields of products than unhindered substrates **135b**.

Table 26: Substrate scope for alkenylations of *meta*- and *para*-substituted *N*-tosylbenzamides.[a]



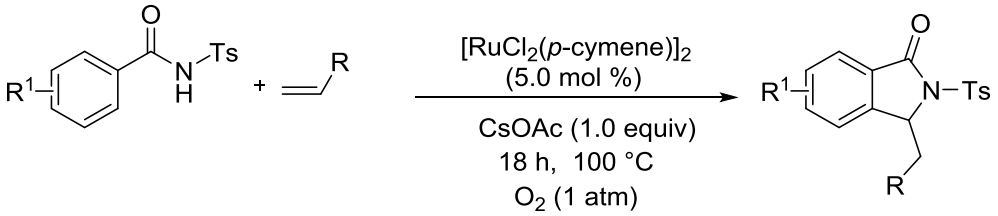
135 **17** **136**

entry	substrate 135	alkene 17	product 136	yield [%]	yield [%][b]
1				68	86
	135b	**17c**	**136bc**		
2				80	69
	135b	**17d**	**136bd**		
3				52	40
	135b	**17f**	**136bf**		
4				54	77
	135g	**17c**	**136gc**		

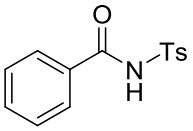
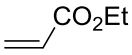
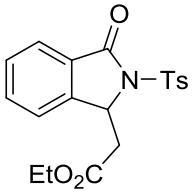
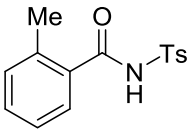
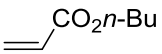
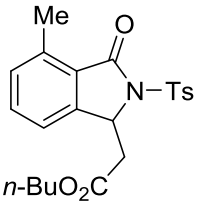
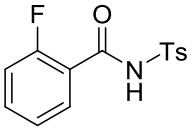
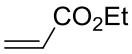
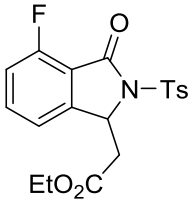
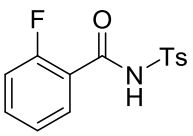
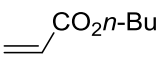
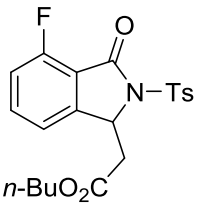
[a] General reaction conditions: **135** (0.50 mmol), **17** (2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), CsOAc (0.50 mmol), 100 °C, 18 h, O_2 (1 atm), yields of isolated products; [b] KOAc (2.50 mmol).

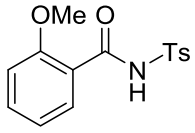
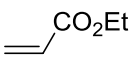
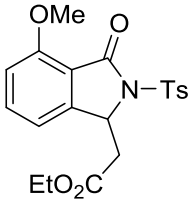
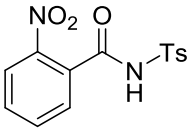
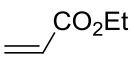
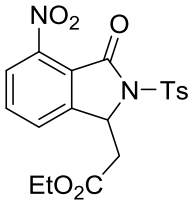
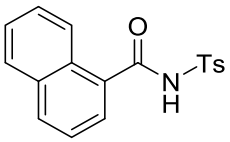
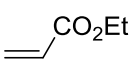
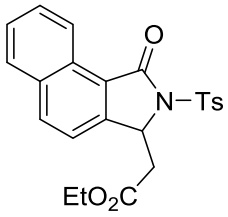
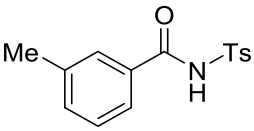
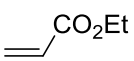
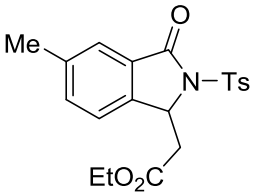
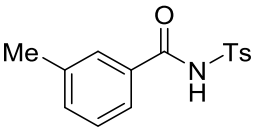
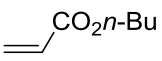
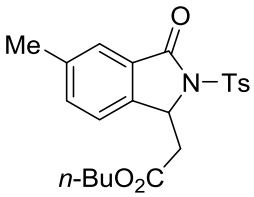
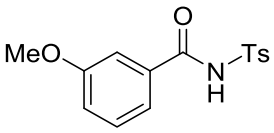
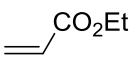
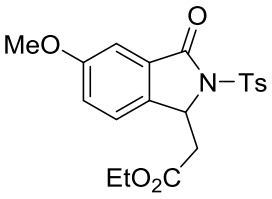
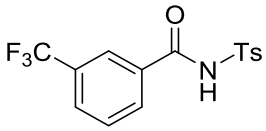
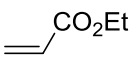
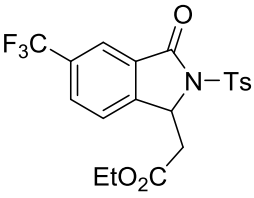
With the optimized catalytic system in hand, we evaluated the scope of the aerobic C−H/N−H bond functionalization (Table 27). *Ortho*-, *meta*- and *para*-substituted *N*-tosylbenzamides **135** were efficiently converted into the corresponding isoindolinones **136**. We were pleased to find that various important electrophilic functional groups, such as nitro- or chloro- moieties, were well tolerated under the optimized reaction conditions.

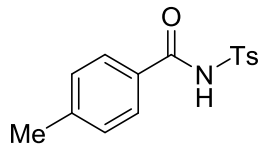
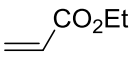
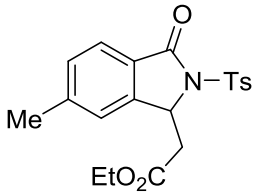
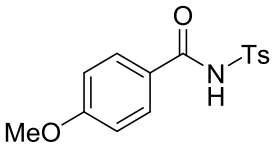
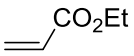
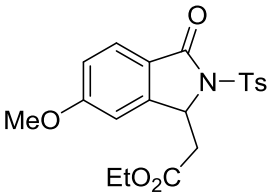
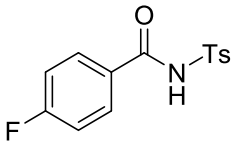
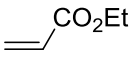
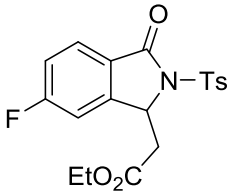
Table 27: Substrate scope for alkenylations of *meta*- and *para*-substituted *N*-tosylbenzamides **135**.[a]



135 **17** **136**

entry	substrate 135	alkene 17	product 136	yield [%]
1				53
	135a	**17c**	**136ae**	
2				56
	135b	**17e**	**136be**	
3				85
	135c	**17c**	**136cc**	
4				58
	135c	**17e**	**136ce**	

5				52
	135d	**17c**	**136dc**	
6				45
	135f	**17c**	**136fc**	
7				45
	135e	**17c**	**136ec**	
8				65
	135h	**17c**	**136he**	
9				47
	135h	**17e**	**136he**	
10				60
	135i	**17c**	**136ic**	
11				48

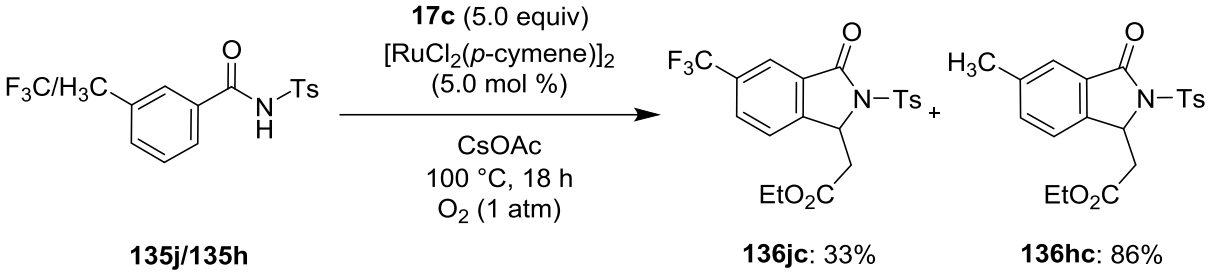
	135j	**17c**	**136jc**	
12				60
	135k	**17c**	**136kc**	
13				59
	135l	**17c**	**136lc**	
14				59
	135m	**17c**	**136mc**	

[a] General reaction conditions: **135** (0.50 mmol), **17** (2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), CsOAc (0.50 mmol), 100 °C, 18 h, O_2 (1 atm), yields of isolated products.

3.5.3 Mechanistic Studies

3.5.3.1 Intermolecular Competition Experiment

The competition experiment between the *meta*-substituted trifluoromethyl substrate **135j** and the methyl analogue **135h** revealed that the electron-rich substrate **135h** are preferred for this alkene annulation reaction (Scheme 3.18). This reactivity pattern is in accordance with the results of previously published oxidative alkyne annulation reactions.[59]

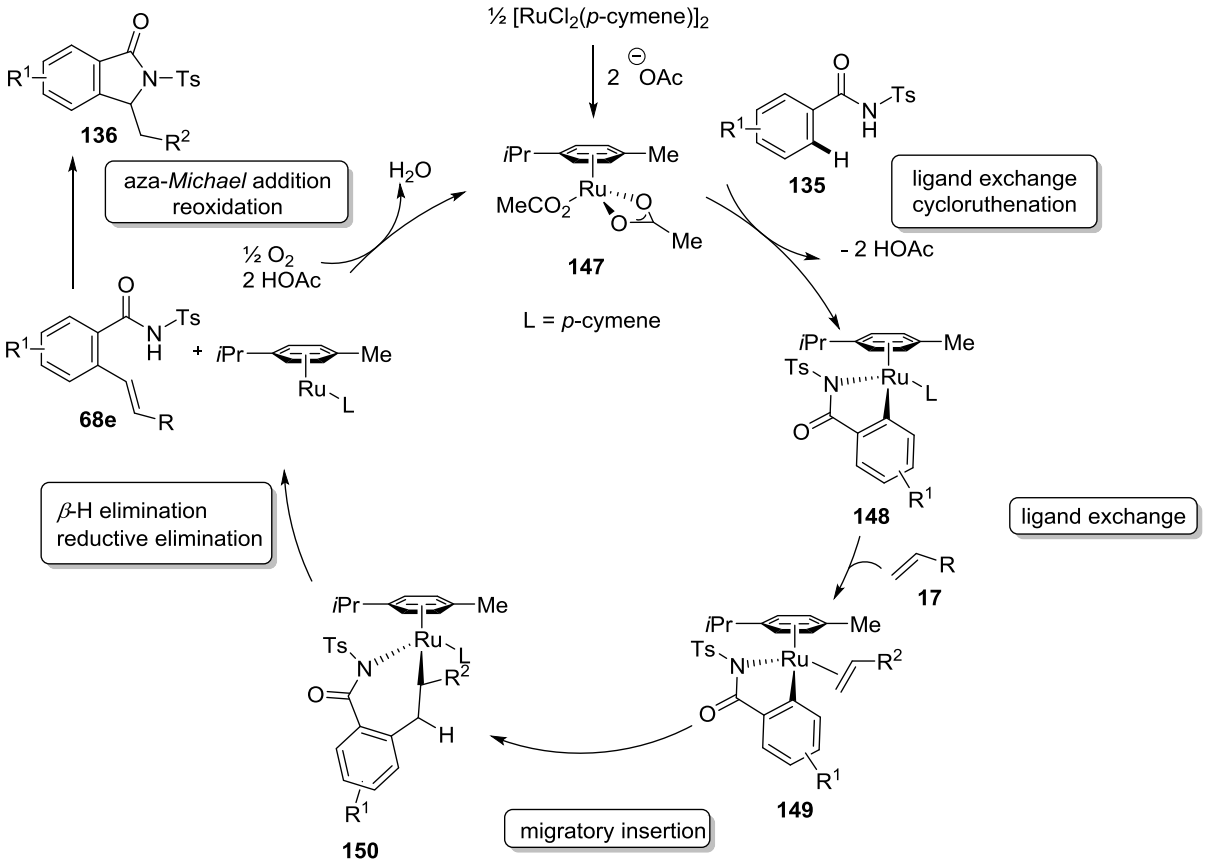


135j/135h **136jc**: 33% **136hc**: 86%

Scheme 3.18: Intermolecular competition experiment.

3.5.3.2 Proposed Catalytic Cycle

Based on these mechanistic studies we propose the catalytic cycle to involve an initial cyclo-ruthenation with the ruthenium(II) bisacetate complex **147** (Scheme 3.19). Thereby, ruthenacycle **148** is generated, along with two equivalents of acetic acid. Afterwards, coordination and migratory insertion of the alkene **17** results in the seven-membered ruthenacycle **149**. The intermediate **150** undergoes *β*-hydride elimination, to yield the alkenylated *N*-tosylbenzamide. Thereafter, the nucleophilic cyclization resulted in the desired isoindolinone **136** and water as the sole by-product. Reoxidation of the catalyst ruthenium(0) species with oxygen regenerates the catalytic reactive ruthenium species.

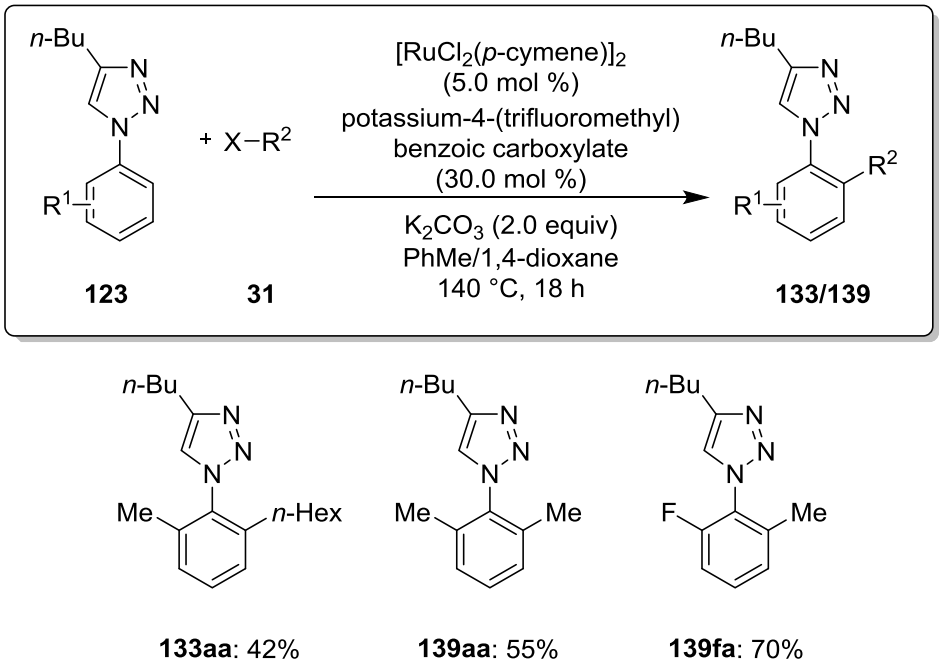


Scheme 3.19: Proposed catalytic cycle for alkene annulation with oxygen.

In summary, this ruthenium(II)-catalyzed oxidative alkenylation reaction is the most economical way to synthesize isoindolinones. In comparison, with the reaction with stoichiometric amounts of $Cu(OAc)_2 \cdot H_2O$ there are advantages and disadvantages. With the *ortho*-substituted substrates the yield is higher using copper acetate as an oxidant. With the *para*-substituted substrates the relation is vice versa. In addition, the overall reaction time is shorter for the aerobic reaction. No Cu(OAc) by-poduct, but an excess of substrate thus far is required.

4 Summary and Outlook

The first project focused on the alkylation of biologically active *N*-aryl-1,2,3-triazoles **123**. In spite of detailed screening efforts, the alkylation of these substrates resulted in only moderate yields, which is due to some interfering side-reactions. Promising results were, however, achieved in the methylation of the *N*-aryl-1,2,3-triazoles **123** (Scheme 4.1).

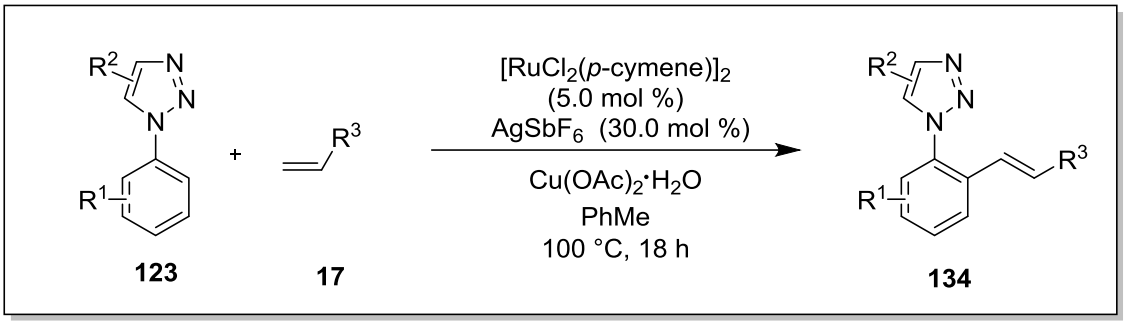


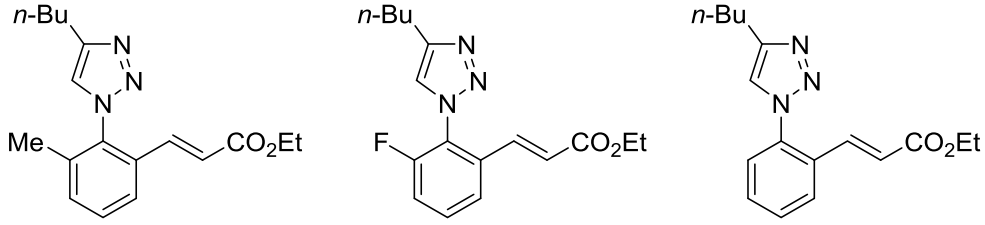
Scheme 4.1: Ruthenium(II)-catalyzed alkylation of *N*-aryl-1,2,3-triazoles.

The main disadvantage of this reaction is the set up, which has to be accomplished under completely inert conditions for yet unknown reason. This renders the reaction less user-friendly and is an aspect that has to be improved. The alkylation reaction with *β*-hydrogen containing unactivated alkyl halides remains challenging. Thus, the reaction conditions have to be further optimized.

The second part of this thesis deals with the extension of the ruthenium-catalyzed alkenylation reaction on the pharmaceutical valuable *N*-aryl-1,2,3-triazoles **123**, which could be successfully established. The optimized ruthenium-catalytic system using $Cu(OAc)_2 \cdot H_2O$ monohydrate as the oxidant tolerated various functional groups (Scheme 4.2).[109]

[109] C. Tirler, L. Ackermann, *Tetrahedron (Symposia in print),* **2015**, *71*, 4543−4551.

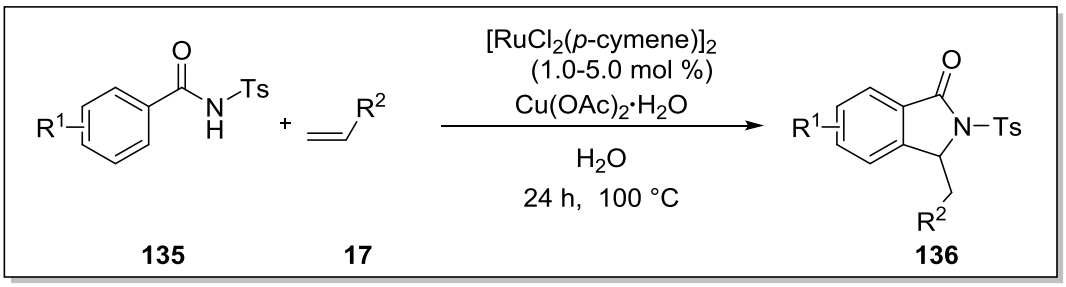


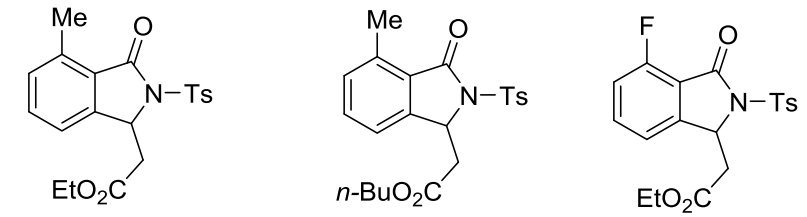


134ac: 82% **134fc**: 60% **134bc**: 71%

Scheme 4.2: Ruthenium-catalyzed alkenylation of *N*-aryl-1,2,3-triazoles.

In the next part, isoindolinones **136** were efficiently synthesized by alkene annulations with acrylates **17** using *N*-tosylbenzamides **135** as the starting materials (Scheme 4.3). Impressively, the reaction could be accomplished with only 1.0 mol % of catalyst loading.





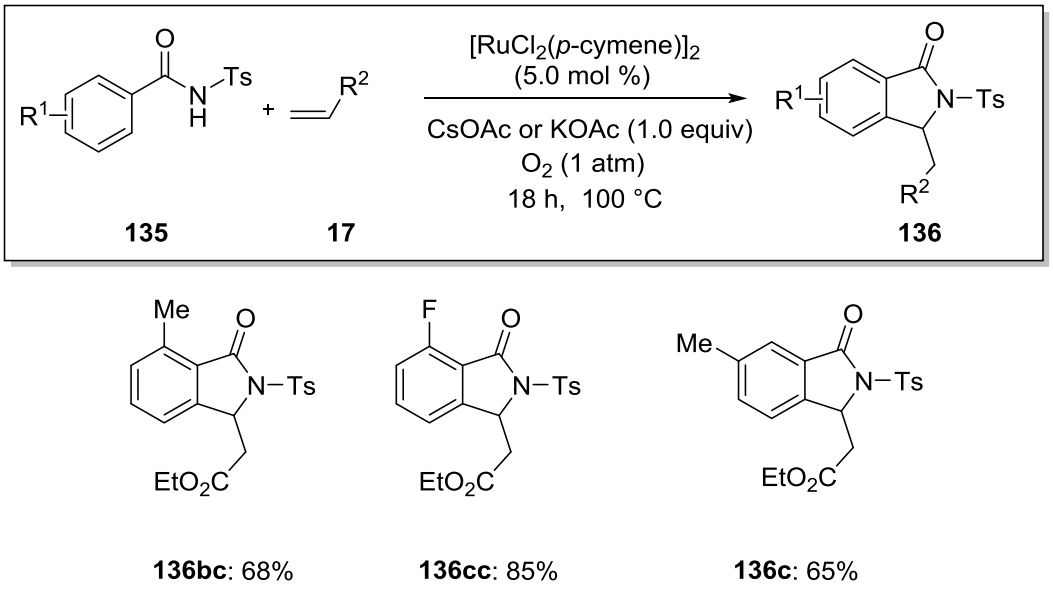
136bc	**136be**	**136cc**
52% (1.0 mol % cat.)	45% (1.0 mol % cat.)	59% (1.0 mol % cat.)
64% (2.0 mol % cat.)	67% (2.0 mol % cat.)	71% (2.5 mol % cat.)
74% (5.0 mol % cat.)	88% (5.0 mol % cat.)	78% (5.0 mol % cat.)

Scheme 4.3: Ruthenium(II)-catalyzed annulation of *N*-tosylbenzamides.

The *N*-tosyl group of the isoindolinone **136af** proofed to be easily cleaved in a traceless fashion to give the free isoindolinones **136n**.

However, this established catalytic system produces Cu(OAc) as stoichiometric waste and could be even more ecologically, avoiding these by-products. This challenge was addressed in the final part of this thesis. Thus we devised reaction conditions as far the use of the most economical terminal oxidant oxygen for the synthesis of isoindolinones producing water as the sole by-product (Scheme 4.4).

This was achieved under conditions, avoiding the use of solvent waste.



Scheme 4.4: Ruthenium(II)-catalyzed annulation of *N*-tosylbenzamides with oxygen as oxidant.

5 Experimental Section

5.1 General Remarks

All reactions involving moisture- or air-sensitive reagents were performed under a N_2 atmosphere using pre-dried glassware and standard Schlenk techniques. Syringes for handling of dry solvents were flushed with dry nitrogen threefold prior to their use.

Vacuum

The following pressures were measured on the used vacuum pump and were not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

Melting points

Melting points were measured using a *Stuart® Melting Point Apparatus SMP3* from BARLOWORLD SCIENTIFIC. Reported values are uncorrected and are given as a range (M.r.), if the melting did not occurr at a specific melting point (M.p.).

Chromotography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F-plates (MACHERY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under UV-light. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040−0.063 mm and 0.063−0.200 mm, 70-230 mesh estimated).

Gas Chromatography

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using *G1800C GCDplus* with mass detector *HP 5971, 5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A GC-System* with mass *detector 5975C (Triplex-Axis-Detector*) from AGILENT TECHNOLOGIES equipped with *HP-5MS* columns (30 m x 0.25 mm x 0.25 µm) were used.

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy was performed at 250, 300 or 600 MHz (^{1}H-NMR), 75.5 or 125 MHz (^{13}C-NMR, APT) and 282 MHz (^{19}F-NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as *δ*-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak.

	^{1}H-NMR	^{13}C-NMR
$CDCl_3$:	7.26 ppm	77.0 ppm
DMSO-D_6:	249 ppm	49.5 ppm

For characterization of the observed resonance multiplicities the following abbrevationsd were applied: s (singlet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), td (doublet of triplet), or analogue representations. The coupling constants *J* are given in Hertz (Hz).

Infrared spectroscopy

Infrared spectra were recorded on a BRUKER *Alpha-P* ATR-spectrometer. Liquid probes have been measured as film and solid probes neat. Analysis of the spectral data has been done by using the OPUS 3.1 software from BRUKER, respectively *OPUS 6*. Absorption ($\tilde{\nu}$) is given in wave numbers (cm^{-1}). Spectra were recorded in the range of 4000 to 400 cm^{-1}.

Mass spectrometry

EI- and EI-HR-MS spectra were measured on a *Time-of-Flight* mass spectrometer *AccuTOF* from JOEL. ESI-mass spectra were recorded on an *Ion-Trap* mass spectrometer *LCQ* from FINNIGAN or on a *Time-of Flight* mass spectrometer *microTOF* from BRUKER. ESI-HR-MS spectra were recorded on a BRUKER *APEX IV* or a BRUKER *DALTONIC* (7T, Transform Ion Cyclotron Resonance (FTCIR)) mass spectrometer. The ratios of mass to charge are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to the following standard procedures.

Solvent	drying Method
tert-Amylalcohol	was stirred over Na chips for 5 h at 120 °C and distilled under ambient pressure.
Dichloromethane	was purified using a solvent purification system (SPS) from MBRAUN.
N,N-Dimethylformamide	was dried over CaH_2 for 8 h, degassed and distilled under reduced pressure.
N-Methyl-2-pyrrolidine	was stirred for 4 h at 150 °C over CaH_2 and subsequently distilled under reduced pressure
Methanol	was stirred over Mg chips for 3 h at 65 °C prior distillation.
Tetrahydrofuran	was purified using SPS solvent purification system from MBRAUN.
Toluene	was either pre-dried over KH followed by distillation from sodium benzophenone ketyl or purified using a solvent purification system MBRAUN.
Water	was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure.
1,4-Dioxane	was dried by distillation from sodium benzophenone ketyl.

Reagents

Chemicals obtained from commercial sources with purity above 95% were used without purification.

The following compounds were synthesized according to known literature procedures and were pure by comparison with the published analytical data:

Potassium 4-(trifluormethyl)benzoate **137**,[110] potassium-3-(trifluoromethyl)benzoate,[111] *N*-aryl-1,2,3-triazoles **123**,[111] 1-phenyl-1*H*-benzo[*d*][1,2,3]triazole **123r**,[112] 3-iodo-1-methyl-

[110] L. J. Gooßen, N. Rodríguez, P. P. Lange, C. Linder, *Angew. Chem. Int. Ed.* **2010**, *49*, 1111–1114
[111] J. Andersen, S. Bolving, X. Liang, *Synlett*, **2005**, *19*, 2941−2947.
[112] L. Alakonda, M. Periasamy, *Synthesis*, **2012**, *44*, 1063–1068.

1*H*-indole **123q**,[113] *N*-tosylbenzamides **135**,[114] *N*-methyl-*N*-tosylacetamide,[115] *N*-tosylacetamide,[116] methyl 4-methylbenzenesulfonate.[117]

The following compounds were used with the kind permission of the persons named below:

Karsten Rpauch: $[RuCl_2(p\text{-cymene})]_2$, $[Ru(O_2CMes)_2(p\text{-cymene})]$.

Dr. Jie Li: Pivaloylalanine

Dr. Marvin Schinkel: KO_2CAd.

Dr. Karolina Graczyk: KO_2CMes.

Dr. Emelyne Diers: Diethyl vinylphosphonate.

Prof. Dr. Ingo Krossing, Freiburg University: $Ag[Al(OC\{CF_3\}_3)_4]$.

[113] (a) V. Bocchi, G. Palla, *Synthesis* **1982,** 1096; (b) F. De Simone, T. Saget, F. Benfatti, S. Almeida, J. Waser, *Chem. Eur. J.* **2011**, *17*, 14527–14538.
[114] F. Peron, *Chem. Eur. J.* **2014***, 20*, 7507–7513
[115] Y. Inamoto, Y. Kaga, Y. Nishimoto, M. Yasuda, A. Baba, *Org. Lett.* **2013**, *15,* 3452−3455.
[116] M. V. Pham, B. Ye, N. Cramer, *Angew. Chem . Int. Ed.* **2012**, *51*, 10610–10614.
[117] A. R. Massah, M. Javaherian, F. Kazemi, *Tetrahedron*, **2007**, *63*, 5083–5087.

5.2 General Procedures

General Procedure A: Copper-Catalyzed Synthesis of 1,4-Disubstituted Triazoles 123

To a solution of DMSO/H_2O (3 mL/mmol, 5:1), sodium azide (1.1 equiv), aryliodide (**1**) (1.0 equiv), 1-hexyne (1.0 equiv), CuI (10.0 mol %), sodium ascorbate (10.0 mol %) and *N*,*N*'-dimethylendiamine (15.0 mol %) were added sequentially. The mixture was stirred over night at 55 °C. H_2O (5 mL/mmol) and CH_2Cl_2 (5 mL/mmol) were added to the reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL/mmol). The combined organic layers were washed with H_2O and a mixture of sat. aq. NH_4Cl/NH_3 (1:1) until the disappearance of the blue color, as well as washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield the triazoles **123**.

General Procedure B: General Procedure for the Preparation of Substituted *N*-Tosylbenzamides 135

Oxalylchloride (1.2 equiv) and DMF (1 drop) were added to a stirred solution of acid (1.1 equiv) in dry toluene (0.8 mL/mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred at ambient temperature until no bubbles were observed. The reaction mixture was directly used in the next step.
The acid chloride in dry toluene was added dropwise over 15 min to a stirred solution of *p*-toluene sulfonamide (1.0 equiv), NEt_3 (2.5 equiv) and DMAP (0.5 mol %) in EtOAc (2 mL/mmol). The reaction mixture was stirred at 55 °C for 1 h under a nitrogen atmosphere, cooled to ambient temperature and quenched with a solution of aqueous HCl (0.5 M, 3 mL/mmol). The resulting mixture was then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by passing through a pad of silica gel, eluting with CH_2Cl_2 and concentrated under reduced pressure. The residue was purified by recrystallization in EtOH to give the tosylamides **135**.

Representative Procedure C: Ruthenium(II)-Catalyzed Alkylation of Substituted *N*-Aryl-1,2,3-triazoles 133

A suspension of *N*-aryl-1,2,3-triazoles **123** (1.00 mmol, 1.0 equiv), alkyl bromide **40** (3.00 mmol, 3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 0.05 mmol, 5.0 mol %), K_2CO_3 (267.0 mg, 2.00 mmol, 2.0 equiv) and 4-(trifluormethyl)benzoate (68.9 mg, 0.30 mmol,

30.0 mol %) in 1,4-dioxane (4 mL), was stirred at 140 °C for 18 h under N_2. At ambient temperature, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc).

Representative Procedure D: Ruthenium(II)-Catalyzed Methylation of Substituted *N*-Aryl-1,2,3-triazoles 139

In a pre-dried sealed tube, *N*-aryl-1,2,3-triazoles **123** (1.00 mmol, 1.0 equiv), methyl iodide **41a** (442 mg, 3.00 mmol, 3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 0.05 mmol, 5.0 mol %), K_2CO_3 (267.0 mg, 2.00 mmol, 2.0 equiv) and 4-(trifluormethyl)benzoate (68.9 mg, 0.30 mmol, 30.0 mol %) in 1,4-dioxane (4 mL) or toluene (4 mL), were set up in the glovebox. The reaction mixture was stirred at 140 °C for 18 h under N_2 atmosphere. At ambient temperature, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc).

Representative Procedure E: Ruthenium(II)-Catalyzed Oxidative Alkenylation with Substituted *N*-Aryl-1,2,3-triazoles 134

A suspension of *N*-aryl-1,2,3-triazoles **123** (1.00 mmol, 1.0 equiv), acrylate **17** (1.5−3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (239.8 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30.0 mol %) in toluene (4 mL), was stirred at 100 °C for 18 h under N_2. At ambient temperature, the reaction mixture was diluted with sat. aq. NH_4Cl/NH_3 (1:1, 10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc).

Representative Procedure F: Synthesis of Isoindolinones 136 *via* Ruthenium(II)-Catalyzed C−H/N–O-Bond Functionalization

A suspension of *N*-tosylbenzamides **135** (1.00 mmol, 1 equiv), acrylate **17** (1.50−3.00 mmol, 1.5−3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.01−0.05 mmol, 1.0−5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.7 mg, 2.10 mmol, 2.1 equiv) in H_2O (5 mL), was stirred at 100 °C for 24 h under air. At ambient temperature, the reaction mixture was diluted with sat. aq. NH_4Cl/NH_3 (1:1, 10 mL) and EtOAc (10 mL). The separated aqueous phase was extracted with EtOAc (2 x 25 mL/mmol). The combined organic layers were washed with H_2O and a mixture of sat. aq. NH_4Cl/NH_3 (1:1) until the disappearance of the blue color, as well as with brine (50 mL)

and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

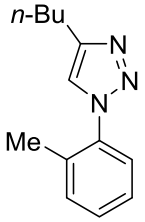
Representative Procedure G: Synthesis of Isoindolinones 136 *via* Aerobic Ruthenium(II)-Catalyzed C−H/N–O-Bond Functionalization

A suspension of *N*-tosylbenzamides **135** (1.00 mmol, 1 equiv), acrylate **17** (5.00 mmol, 5.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 0.05 mmol, 5.0 mol %) and MOAc (1.00 mmol, 1.0 equiv) was stirred at 100 °C for 18 h under an oxygen atmosphere. At ambient temperature, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc). At ambient temperature, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc).

5.3 Experimental Procedures and Analytical Data

5.3.1 Synthesis of *N*-Aryl-1,2,3-triazoles

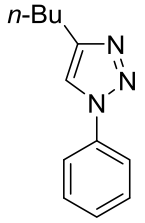
Synthesis of 4-*n*-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (123a):



The general procedure **A** was followed using 1-iodo-2-methylbenzene (**1d**) (4.36 g, 20 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123a** (2.94 g, 63%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.43–7.27 (m, 4H), 2.90–2.73 (m, 2H), 2.20 (s, 3H), 1.83–1.63 (m, 2H), 1.54–1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.3 (C_q), 136.9 (C_q), 133.8 (C_q), 131.5 (CH), 129.7 (CH), 126.9 (CH), 126.1 (CH), 122.4 (CH), 31.6 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 18.0 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2956, 2929, 2860, 1552, 1502, 1214, 1117, 1039, 988, 760 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 238 (2) [M+Na$^+$], 216 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}N_3$, [M+H$^+$] 216.1495, found 216.1507.
The spectral data are in accordance with those reported in the literature.[15c]

Synthesis of 4-*n*-Butyl-1-phenyl-1*H*-1,2,3-triazole (123b)



The general procedure **A** was followed using 1-iodo-benzene (**1e**) (2.01 g, 10.0 mmol), 1-hexyne (0.82 g, 10.0 mmol), NaN_3 (0.68 g, 10.5 mmol), CuI (0.38 g, 1.0 mmol) and

DMEDA (0.26 g, 1.5 mmol). Purification by column chrommatography (*n*-pentane/EtOAc 5/1) yielded **123b** (1.57 g, 78%) as a colorless solid.

M.r.: 58−59 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.86−7.33 (m, 6H), 2.55 (t, J = 7.4 Hz, 2H), 1.53−1.35 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.3 (C_q), 130.5 (C_q), 128.5 (CH), 127.9 (CH), 126.6 (CH), 119.4 (CH), 50.1 (CH_2), 32.4 (CH_2), 19.7 (CH_2), 14.4 (CH_3).

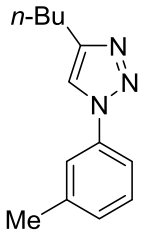
IR (ATR): $\tilde{\nu}$ = 3109, 2988, 2845, 1576, 1475, 1135, 789, 684 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 202 (100) [M+H$^+$].

HR-MS (EI) *m/z* calcd for $C_{16}H_9N_3$, [M$^+$] 188.1188, found 243.1184.

The spectral data are in accordance with those reported in the literature.[118]

Synthesis of 4-*n*-Butyl-1-(*m*-tolyl)-1*H*-1,2,3-triazole (123c)



The general procedure **A** was followed using 1-iodo-3-methylbenzene (**1f**) (4.36 g, 20 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123c** (2.94 g, 63%) as an orange solid.

M.r.: 44−45 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.70 (s, 1H), 7.55–7.18 (m, 1H), 7.49–7.41 (m, 1H), 7.33 (dd, J = 7.8, 7.8 Hz, 1H), 7.20–7.15 (m, 1H), 2.82–2.70 (m, 2H), 2.40 (s, 3H), 1.77–1.52 (m, 2H), 1.40 (dq, J = 14.5, 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 149.1 (C_q), 139.9 (C_q), 137.3 (C_q), 129.5 (CH), 129.2 (CH), 121.1 (CH), 118.9 (CH), 117.5 (CH), 31.6 (CH_2), 25.5 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 13.7 (CH_3).

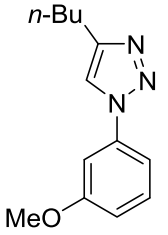
IR (ATR): $\tilde{\nu}$ = 3123, 2931, 1591, 1494, 1225, 1046, 903, 851, 828, 784 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 254 (39) [M+K$^+$], 238 (26) [M+Na$^+$], 216 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}N_3$, [M+H$^+$] 216.1495, found 216.1502.

[118] Y. D. Bidal, M. Lesieur, M. Melaimi, D. B. Cordes, A. M. Z. Slawin, G. Bertrand, C. S. J. Cazin, Chem. Commun. **2015**, 51, 4778−4781.

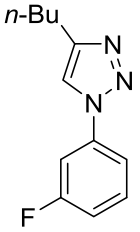
Synthesis of 4-*n*-Butyl-1-(3-methoxyphenyl)-1*H*-1,2,3-triazole (123d)



The general procedure **A** was followed using 1-iodo-3-methoxybenzene (**1g**) (2.18 g, 9.3 mmol), 1-hexyne (0.82 g, 10.0 mmol), NaN_3 (0.68 g, 10.5 mmol), CuI (0.38 g, 1.0 mmol) and DMEDA (0.26 g, 1.5 mmol). Purification by column chrommatography (*n*-pentane/EtOAc 5/1) yielded **123d** (2.00 g, 93%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.70 (s, 1H), 7.36 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.31 (dd, *J* = 2.3, 2.3 Hz, 1H), 7.24–7.18 (m, 1H), 6.91 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.84 (s, 3H), 2.88–2.62 (m, 2H), 1.77–1.59 (m, 2H), 1.40 (ddt, *J* = 14.5, 9.3, 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 160.6 (C_q), 149.2 (C_q), 138.4 (C_q), 130.5 (CH), 119.0 (CH), 114.3 (CH), 112.3 (CH), 106.3 (CH), 55.7 (CH_3), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2955, 2929, 2859, 1608, 1595, 1497, 1461, 1292, 1255, 1155 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 270 (61) [M+K^+], 254 (26) [M+Na^+], 232 (100) [M+H^+].
HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}N_3O$, [M+H^+] 232.1444, found 232.1436.

Synthesis of 4-*n*-Butyl-1-(3-fluorophenyl)-1*H*-1,2,3-triazole (123e)



The general procedure **A** was followed using 1-fluoro-3-iodobenzene (**1h**) (4.40 g, 20.0 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123e** (3.77 g, 86%) as an orange solid.

M.p.: 41 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.54–7.38 (m, 3H), 7.16–7.02 (m, 1H), 2.86–2.68 (m, 2H), 1.70 (dddd, J = 8.7, 7.5, 7.0, 5.8 Hz, 2H), 1.52–1.29 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 163.2 ($^1J_{C\text{-}F}$ = 248.4 Hz, C_q), 149.3 (C_q), 138.5 ($^3J_{C\text{-}F}$ = 10.1 Hz, C_q), 131.1 ($^3J_{C\text{-}F}$ = 9.0 Hz, CH), 118.7 (CH), 115.7 ($^4J_{C\text{-}F}$ = 3.3 Hz, CH), 115.3 ($^2J_{C\text{-}F}$ = 21.2 Hz, CH), 108.1 ($^2J_{C\text{-}F}$ = 26.3 Hz, CH), 31.3 (CH_2), 25.2 (CH_2), 22.2 (CH_2), 13.7 (CH_3).

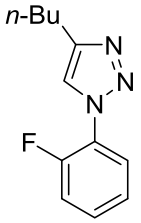
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -110.1 (ddd, J = 9.3, 8.1, 5.7 Hz).

I**R** (ATR): $\tilde{\nu}$ = 3137, 2956, 2872, 1601, 1499, 1469, 1242, 1223, 1144, 1046 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 258 (33) [M+K$^+$], 242 (33) [M+Na$^+$], 220 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{12}H_{15}FN_3$, [M+H$^+$] 220.1245, found 220.1240.

Synthesis of 4-*n*-Butyl-1-(2-fluorophenyl)-1*H*-1,2,3-triazole (123f)



The general procedure **A** was followed using 1-fluoro-2-iodobenzene (**1i**) (4.40 g, 20.0 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123f** (3.77 g, 86%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01–7.82 (m, 1H), 7.78 (dd, J = 3.0, 0.7 Hz, 1H), 7.46–7.30 (m, 1H), 7.31–7.18 (m, 2H), 2.77 (ddd, J = 7.9, 7.3, 0.8 Hz, 2H), 1.69 (dddd, J = 8.8, 7.7, 7.1, 5.8 Hz, 2H), 1.50–1.26 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 153.4 ($^1J_{C\text{-}F}$ = 250.3 Hz, C_q), 148.9 ($^5J_{C\text{-}F}$ = 1.2 Hz, C_q), 129.9 ($^3J_{C\text{-}F}$ = 7.9 Hz, CH), 125.6 ($^2J_{C\text{-}F}$ = 10.1 Hz, C_q), 125.3 ($^4J_{C\text{-}F}$ = 3.8 Hz, CH), 124.9 (CH), 122.0 ($^3J_{C\text{-}F}$ = 8.2 Hz, CH), 117.0 ($^2J_{C\text{-}F}$ = 20.1 Hz, CH), 31.5 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

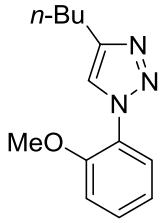
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -121.0–-121.5 (m).

IR (ATR): $\tilde{\nu}$ = 2956, 2930, 2860, 1597, 1508, 1473, 1274, 1225, 1110, 1940 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 242 (22) [M+Na$^+$], 220 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{12}H_{14}FN_3Na$, [M+Na$^+$] 242.1064, found 242.1064.

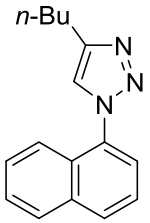
Synthesis of 4-*n*-Butyl-1-(2-methoxyphenyl)-1*H*-1,2,3-triazole (123g)



The general procedure **A** was followed using 1-iodo-2-methoxybenzene (**1j**) (2.34 g, 10.0 mmol), 1-hexyne (0.82 g, 10.0 mmol), NaN_3 (0.68 g, 10.5 mmol), CuI (0.38 g, 1.0 mmol) and DMEDA (0.26 g, 1.5 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123g** (2.06 g, 89%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.71 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H), 7.08−7.00 (m, 2H), 3.84 (s, 3H), 2.84–2.67 (m, 2H), 1.79–1.61 (m, 2H), 1.40 (dp, *J* = 9.4, 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 151.2 (C_q), 147.7 (C_q), 129.8 (CH), 126.6 (C_q), 125.5 (CH), 122.9 (CH), 121.2 (CH), 112.3 (CH), 56.0 (CH_3), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2930, 2859, 1601, 1504, 1473, 1285, 1252, 1285, 1252, 1176 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 254 (17) [M+Na$^+$], 232 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}N_3O$, [M+H$^+$] 232.1444, found 232.1444.
The spectral data are in accordance with those reported in the literature.[15c]

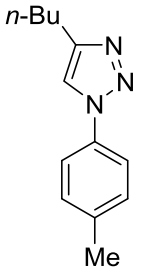
Synthesis of 4-*n*-Butyl-1-(naphthalen-1-yl)-1*H*-1,2,3-triazole (123h)



The general procedure **A** was followed using 1-iodonaphthalene (**1k**) (5.08 g, 20.0 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123h** (4.03 g, 80%) as an orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99–7.84 (m, 2H), 7.68–7.57 (m, 2H), 7.57–7.45 (m, 4H), 2.95–2.81 (m, 2H), 1.87–1.69 (m, 2H), 1.55–1.38 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.4 (C_q), 134.2 (C_q), 134.0 (C_q) 130.1 (CH), 128.7 (C_q), 128.3 (CH), 127.8 (CH), 127.0 (CH), 125.0 (CH), 123.5 (CH), 123.4 (CH), 122.5 (CH), 31.6 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 13.7 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3056, 2929, 2858, 1597, 1512, 1470, 1429, 1219, 1038, 800, 771, 434 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 290 (87) [M+K$^+$], 274 (28) [M+Na$^+$], 252 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{16}H_{18}N_3$, [M+H$^+$] 252.1495, found 252.1484.

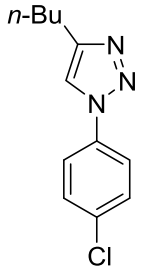
Synthesis of 4-*n*-Butyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole (123i)



The general procedure **A** was followed using 1-iodo-4-methylbenzene (**1l**) (2.18 g, 10.0 mmol), 1-hexyne (0.82 g, 10.0 mmol), NaN_3 (0.68 g, 10.5 mmol), CuI (0.38 g, 1.0 mmol) and DMEDA (0.26 g, 1.5 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123i** (1.64 g, 76%) as a colorless solid.

M.r.: 63−64 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 2.84–2.70 (m, 2H), 2.38 (s, 3H), 1.77–1.61 (m, 2H), 1.40 (dq, J = 14.4, 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 149.1 (C_q), 138.5 (C_q), 135.1 (C_q), 130.2 (CH), 120.4 (CH), 118.9 (CH), 31.7 (CH_2), 25.5 (CH_2), 22.4 (CH_2), 21.0 (CH_3), 13.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3130, 3085, 2922, 2869, 1523, 1456, 1320, 1230, 1198, 1120 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 238 (20) [M+Na$^+$], 216 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}N_3$, [M+H$^+$] 216.1495, found 216.1495.

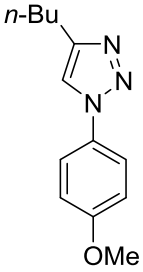
Synthesis of 4-*n*-Butyl-1-(chlorophenyl)-1*H*-1,2,3-triazole (123j)



The general procedure **A** was followed using 1-chloro-4-iodobenzene (**1m**) (4.77 g, 20.0 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123j** (4.10 g, 87%) as a colorless solid.

M.r.: 73−74 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.70–7.60 (m, 3H), 7.49–7.41 (m, 2H), 2.82–2.74 (m, 2H), 1.70 (dddd, *J* = 8.7, 7.6, 7.0, 5.8 Hz, 2H), 1.51–1.30 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 149.5 (C_q), 135.9 (C_q), 134.2 (C_q), 129.9 (CH), 121.6 (CH), 118.8 (CH), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2961, 2927, 1498, 1462, 1403, 1224, 1092, 1047, 1010, 989 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 274 (27) [M+K$^+$], 258 (56) [M+Na$^+$], 236 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{12}H_{15}ClN_3$, [M+H$^+$] 236.0949, found 236.0938.

Synthesis of 4-*n*-Butyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (123k)

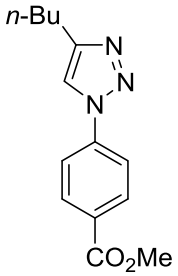


The general procedure **A** was followed using 1-iodo-4-methoxybenzene (**1n**) (2.34 g, 10.0 mmol), 1-hexyne (0.82 g, 10.0 mmol), NaN_3 (0.68 g, 10.5 mmol), CuI (0.38 g, 1.0 mmol) and DMEDA (0.26 g, 1.5 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123k** (2.10 g, 91%) as a colorless solid.

M.r.: 52−53 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.62 (s, 1H), 7.57 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 7.8, 7.8 Hz, 2H), 3.81 (s, 3H), 2.80–2.67 (m, 2H), 1.67 (dddd, *J* = 8.8, 7.6, 7.0, 5.7 Hz, 2H), 1.47–1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.6 (C_q), 148.9 (C_q), 130.8 (C_q), 122.0 (CH), 119.1 (CH), 114.5 (CH), 55.6 (CH_3), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3128, 2955, 2932, 2869, 1516, 1440, 1302, 1245, 1220, 1191 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 254 (25) [M+Na$^+$], 232 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}N_3O$, [M+H$^+$] 232.1444, found 232.1450.

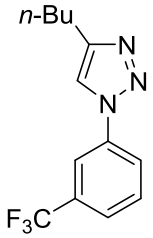
Synthesis of Methyl 4-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)benzoate (123l)



The general procedure **A** was followed using methyl 4-iodobenzoate (**1o**) (4.36 g, 20.0 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123l** (3.23 g, 74%) as a colorless solid.

M.p.: 111 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.79 (s, 1H), 3.94 (s, 3H), 2.80 (ddd, *J* = 7.9, 7.3, 0.7 Hz, 2H), 1.71 (dddd, *J* = 8.7, 7.6, 7.0, 5.7 Hz, 2H), 1.50–1.34 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.1 (C_q), 149.7 (C_q), 140.4 (C_q), 131.4 (CH), 130.0 (C_q), 119.8 (CH), 118.7 (CH), 52.5 (CH_3), 31.5 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3128, 2959, 2929, 2860, 1721, 1607, 1518, 1437, 1280, 1224 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 298 (68) [M+K$^+$], 282 (53) [M+Na$^+$], 260 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{14}H_{18}N_3O_2$, [M+H$^+$] 260.1394, found 260.1388.

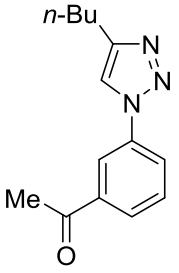
Synthesis of 4-*n*-Butyl-1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazole (123m)



The general procedure **A** was followed using 1-iodo-3-(trifluoromethyl)benzene (**1p**) (5.44 g, 20.0 mmol), 1-hexyne (1.64 g, 20.0 mmol), NaN_3 (1.36 g, 21.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123m** (4.68 g, 87%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01–7.82 (m, 1H), 7.78 (dd, J = 3.0, 0.7 Hz, 1H), 7.46–7.30 (m, 1H), 7.31–7.18 (m, 2H), 2.77 (ddd, J = 7.9, 7.3, 0.8 Hz, 2H), 1.69 (dddd, J = 8.8, 7.7, 7.1, 5.8 Hz, 2H), 1.50–1.26 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 149.8 (C_q), 137.7 (C_q), 132.5 ($^2J_{C\text{-}F}$ = 33.2 Hz, C_q), 130.6 (CH), 125.1 ($^3J_{C\text{-}F}$ = 3.7 Hz, CH), 123.5 ($^4J_{C\text{-}F}$ = 1.2 Hz, CH), 123.5 ($^1J_{C\text{-}F}$ = 273.2 Hz, C_q), 118.8 (CH), 117.3 ($^3J_{C\text{-}F}$ = 3.9 Hz, CH), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -62.9 (s).
IR (ATR): $\tilde{\nu}$ = 3135, 3084, 2958, 2932, 2862, 1600, 1557, 1485, 1461, 1323 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 292 (7) [M+Na^+], 270 (100) [M+H^+].
HR-MS (ESI) *m/z* calcd for $C_{13}H_{15}F_3N_3$, [M+H^+] 270.1213, found 270.1212.

Syntheisis of 1-[3-(4-*n*-Butyl-1*H*-1,2,3-triazol-1-yl)phenyl]ethan-1-one (123n)



The general procedure **A** was followed using 1-(3-iodophenyl) ethan-1-one (**1q**) (2.46 g, 10.0 mmol), 1-hexyne (0.82 g, 10.0 mmol), NaN_3 (0.68 g, 10.5 mmol), CuI (0.38 g, 1.0 mmol) and DMEDA (0.26 g, 1.5 mmol). Purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded **123n** (1.45 g, 60%) as an orange solid.

M.p.: 43 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (dd, J = 1.9, 1.9 Hz, 1H), 8.48–8.38 (m 2H), 8.23 (s, 1H), 8.0 (dd, J = 8.4 Hz, 1H), 3.40–3.17 (m, 2H), 3.10 (s, 3H), 2.27–2.05 (m, 2H), 1.86 (dq, J = 14.5, 7.3 Hz, 2H), 1.39 (t, J = 7.3 Hz, 3H).

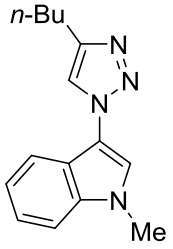
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 196.9 (C_q), 149.7 (C_q), 138.6 (C_q), 137.8 (C_q), 130.3 (CH), 128.2 (CH), 124.8 (CH), 119.6 (CH), 118.9 (CH), 31.6 (CH_2), 26.9 (CH_3), 25.5 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3139, 2957, 2928, 2857, 1682, 1604, 1556, 1490, 1398, 1287 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 238 (16) [M+Na$^+$], 244 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{18}N_3O$, [M+H$^+$] 244.1444, found 244.1450.

Synthesis of 3-(4-*n*-Butyl-1*H*-1,2,3-triazol-1-yl)-1-methyl-1*H*-indole (123o)



The general procedure **A** was followed using 3-iodo-1-methyl-1*H*-indole (**1r**) (3.86 g, 15.0 mmol), 1-hexyne (1,23 g, 15.0 mmol), NaN_3 (1.02 g, 17.0 mmol), CuI (0.29 g, 1.5 mmol) and DMEDA (0.29 g, 2.3 mmol). Purification by column chromatography (*n*-pentane/EtOAc 9/1) yielded **123o** (1.41 g, 37%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.76 (dd, J = 7.9, 1.0 Hz, 1H), 7.67 (s, 1H), 7.41 (d, J = 0.7 Hz, 1H), 7.38–7.27 (m, 2H), 7.25–7.17 (m, 1H), 3.82 (s, 3H), 2.88–2.73 (m, 2H), 1.82–1.65 (m, 2H), 1.45 (dq, J = 14.4, 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).

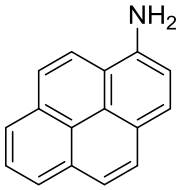
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.3 (C_q), 135.6 (C_q), 123.2 (CH) 121.6 (CH), 121.3 (C_q), 121.0 (CH), 120.9 (CH), 118.6 (CH), 115.2 (C_q), 109.9 (CH), 33.2 (CH_3), 31.7 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 13.7 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2954, 2929, 2858, 1730, 1615, 1478, 1447, 1334, 1247, 1213 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 293 (85) [M+K$^+$], 277 (18) [M+Na$^+$], 255 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{18}N_4$, [M+H$^+$] 255.1604, found 255.1591.

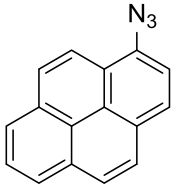
Synthesis of Pyren-1-amine (123pa)



A suspension of 1-nitropyrene (5.55 g, 22 mmol) and palladium on carbon (0.58 g) in EtOAc (85 mL) and HOAc (7 mL, 17.4 M) was stired under a H_2 atmosphere over night at ambient temperature. The reaction mixture was filtered over celite and the solvent was evaporated under reduced pressure. Purification by column chromatography (DCM/*n*-pentane 1/1) yielded **123pa** (4.16 g, 84%) as a green solid.

M.r.: 124−125 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.07 (ddd, *J* = 7.6, 5.8, 1.3 Hz, 2H), 8.03–7.88 (m, 5H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 4.44 (brs, 2H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 141.0 (C_q), 132.3 (C_q), 131.8 (C_q), 127.7 (CH), 126.1 (CH), 126.1 (CH), 126.1 (CH), 126.1 (C_q), 125.6 (C_q), 124.4 (C_q), 124.2 (CH), 123.8 (CH), 123.6 (CH), 120.2 (CH), 117.0 (C_q), 114.1 (CH).
IR (ATR): $\tilde{\nu}$ = 3321, 3206, 3027, 1616, 1598, 1508, 1483, 1432, 1334, 1270 cm^{-1}.
MS (EI) *m/z* (relative intensity): 217 (100) [M^+], 200 (3), 189 (32), 163 (3), 108 (9), 94 (9), 81 (3), 63 (2), 58 (4), 43 (12).
HR-MS (EI) *m/z* calcd for $C_{16}H_{11}N$, [M^+] 217.0891, found 217.0889.

Synthesis of 1-Azidopyren (123pb)



A suspension of pyren-1-amine (4.00 g, 18 mmol) in EtOAc (30 mL) was cooled to 0 °C. HCl (8 mL, 33 M) was added to the reaction mixture at 0 °C. A solution of sodium nitrite (1.66 g, 25 mmol) in H_2O (20 mL) was added dropwise to the cooled reaction mixture over 10 minutes and was stirred for 1 h. Then NaN_3 in H_2O (20 mL) was added to the suspension and stirred for further 4 h at ambient temperatures. The reaction mixture was extracted with

EtOAc (3 x 50 mL), dried over Na_2SO_4. After filtration and evaporation of the solvent *in vacuo*, the crude brown product was used without further purification in the next step.

M.r.: 113−114 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, J = 9.2 Hz, 1H), 8.17–7.90 (m, 7H), 7.72 (d, J = 8.2 Hz, 1H).

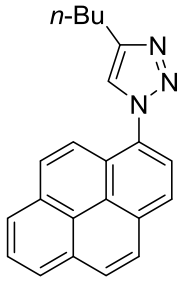
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 133.2 (C_q), 131.6 (C_q), 131.4 (C_q), 128.4 (C_q), 127.6 (CH), 127.2 (CH), 126.8 (CH), 126.5 (CH), 125.6 (CH), 125.5 (CH), 125.3 (C_q), 125.2 (CH), 124.5 (C_q), 122.6 (C_q), 121.6 (CH), 115.4 (CH).

IR (ATR): $\tilde{\nu}$ = 3037, 2156, 2107, 1731, 1597, 1503, 1487, 1457, 1434, 1322 cm^{-1}.

MS (EI) *m/z* (relative intensity): 243 (13) [M$^+$], 214 (100), 200 (3), 187 (22), 163 (5), 107 (14), 93 (23), 81 (3), 74 (3), 63 (3).

HR-MS (EI) *m/z* calcd for $C_{16}H_9N_3$, [M$^+$] 243.0896, found 243.0891.

Synthesis of 4-*n*-Butyl-1-(pyren-1-yl)-1*H*-1,2,3-triazole (123p)



A suspension of 1-azidopyren (4.42 g, 18 mmol), 1-hexyne (1.64 g, 20.0 mmol), CuI (0.38 g, 2.0 mmol) and DMEDA (0.26 g, 3.0 mmol) in DMSO (20 mL) and H_2O (5 mL) was stirred at 55 °C over night. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). Purification by column chromatography (*n*-pentane/EtOAc 9/1) yielded **123p** (0.48 g, 8%) as a brown solid.

M.r.: 103−104 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.23–8.14 (m, 3H), 8.13–7.95 (m, 5H), 7.83 (d, J = 9.2 Hz, 1H), 7.74 (s, 1H), 2.99–2.82 (m, 2H), 1.93–1.75 (m, 2H), 1.52 (dq, J = 14.5, 7.3 Hz, 2H), 1.03 (t, J = 7.3 Hz, 3H).

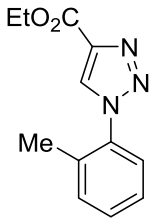
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.6 (C_q), 132.1 (C_q), 131.1 (C_q), 130.8 (C_q), 130.7 (C_q), 129.5 (CH), 128.8 (CH), 127.0 (CH), 126.7 (CH), 126.3 (CH), 126.2 (C_q), 126.0 (CH), 125.0 (C_q), 124.7 (CH), 124.2 (C_q), 123.9 (CH), 123.4 (CH), 121.3 (CH), 31.7 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3130, 2949, 2919, 2851, 1693, 1601, 1459, 1057, 841, 763 cm^{-1}.

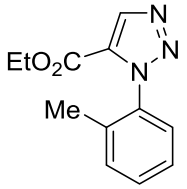
MS (EI) *m/z* (relative intensity): 325 (3) [M^+], 297 (40), 254 (100), 241 (8), 227 (16), 216 (10), 201 (61), 174 (3), 150 (2), 127 (5), 100 (7), 58 (3), 43 (8).
HR-MS (EI) *m/z* calcd for $C_{22}H_{19}N_3$, [M^+] 325.1597, found 325.1573.

Synthesis of Ethyl 1-(*o*-tolyl)-1*H*-1,2,3-triazole-4-carboxylate (123q) and Ethyl 1-(*o*-tolyl)-1*H*-1,2,3-triazole-5-carboxylate (123r)

In a 25 mL microwave flask a mixture of 1-azido-2-methylbenzene (0.67 g, 5 mmol) and ethyl propionate (5.00 g, 50 mmol) were stirred at 100 °C (50W) for 1.5 h. Purification by column chromatography (*n*-pentane/EtOAc 9/1) yielded **123q** (0.05 g, 43%) and **123r** (0.15 g, 13%) as orange oils.[105]



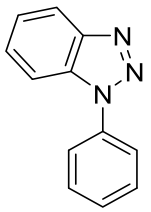
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1H), 7.50–7.29 (m, 4H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 160.9 (C_q), 140.4 (C_q), 135.9 (C_q), 133.8 (C_q), 131.7 (CH), 130.6 (CH), 130.1 (CH), 129.1 (CH), 127.2 (CH), 61.6 (CH_2), 18.0 (CH_3), 14.5 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3133, 2982, 1719, 1541, 1503, 1374, 1335, 1292, 1244, 1226 cm^{-1}.
MS (EI) *m/z* (relative intensity): 231 (7) [M^+], 186 (8), 175 (8), 158 (23), 144 (12), 130 (100), 118 (15), 103 (15), 91 (47), 77 (19), 65 (45), 51 (11), 43 (13).
HR-MS (EI) *m/z* calcd for $C_{12}H_{13}N_3O_2$, [M^+] 231.1008, found 231.1014.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1H), 7.46 (dddd, *J* = 7.3, 1.4, 0.4 Hz, 1H), 7.39–7.21 (m, 2H), 7.26–7.21 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.02 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 157.7 (C_q), 137.7 (CH), 136.2 (C_q), 135.2 (C_q), 130.9 (CH), 130.6 (CH), 130.1 (C_q), 127.1 (CH), 126.6 (CH), 61.9 (CH_2), 17.3 (CH_3), 13.4 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2981, 1730, 1499, 1464, 1367, 1307, 1291, 1277, 1184, 1048 cm^{-1}.
MS (EI) *m/z* (relative intensity): 231 (30) [M^+], 174 (4), 158 (23), 144 (8), 130 (100), 118 (22), 103 (26), 91 (43), 77 (35), 65 (29), 51 (12), 43 (16).

HR-MS (EI) *m/z* calcd for $C_{12}H_{13}N_3O_2$, [M^+] 231.1008, found 231.1009.

Synthesis of 1-Phenyl-1*H*- 4-*n*-Butyl-1*H*-benzo[*d*]1,2,3-triazole (123s)



To a 250-mL schlenk flask, containing a magnetic stirring bar and equipped with an air condenser (without water circulation), were added Fe_2O_3 (399 mg, 10 mol %), 1*H*-benzo[*d*][1,2,3]triazole (2,98 mg, 25 mmol), *t*-BuOK (5.60 g, 50 mmol), DMSO (75 mL), and iodobenzene **1c** (10,2 g, 50 mmol) in an open atmosphere. The contents were stirred for 24 h at 120 °C and allowed to cool to 25 °C. The mixture was diluted with EtOAc (25 mL) and H_2O (25 mL) and stirring was continued for a further 10 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with H_2O, brine and were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (*n*-pentane/EtOAc 9/1) to give **147c** (1.44 g, 30%) as an orange solid.

M.r.: 90−91 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.83–7.78 (m 2H), 7.76 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.66–7.59 (m 2H), 7.58–7.48 (m 2H), 7.44 (ddd, *J* = 8.4, 7.0, 1.0 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 146.7 (C_q), 137.2 (C_q), 132.5 (C_q), 130.0 (CH), 128.8 (CH), 128.4 (CH), 124.5 (CH), 123.0 (CH), 120.5 (CH), 110.5 (CH).

IR (ATR): $\tilde{\nu}$ = 3057, 1595, 1499, 1459, 1447, 1384, 1326, 1291, 1276, 1089 cm^{-1}.

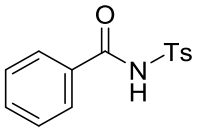
MS (ESI) *m/z* (relative intensity): 218 (25) [M+Na^+], 196 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{12}H_{10}N_3$, [M+H^+] 196.0869, found 196.0871.

The spectral data are in accordance with those reported in the literature.[112]

5.3.2 Synthesis of *N*-Tosylbenzamides

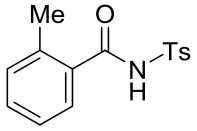
Synthesis of *N*-Tosylbenzamide (135a)



The general procedure **B** was followed using benzoyl chloride (7.80 g, 55.0 mmol, 1.1 equiv) in PhMe (44 mL), *p*-toluene sulfonamide (8.50 g, 50.0 mmol, 1.0 equiv), NEt_3 (12.80 g, 125.0 mmol, 2.5 equiv) and DMAP (3 mg, 0.025 mmol, 0.5 mol %) in EtOAc (100 mL). Recrystallization from EtOH yielded **135a** (9.49 g, 69%) as a colorless solid.

M.p.: 149 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.08 (brs, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.83–7.70 (m, 2H) 7.63–7.50 (m, 1H), 7.46–7.39 (m, 2H), 7.39–7.33 (m, 2H), 2.44 (s, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.3 (C_q), 145.4 (C_q), 135.5 (C_q), 133.6 (CH), 131.3 (C_q), 129.8 (CH), 129.1 (CH), 128.8 (CH), 127.9 (CH), 21.9 (CH_3).
IR (neat): 3309, 1699, 1597, 1494, 1450, 1417, 1333, 1233, 1185, 1162 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 314 (10) [M+K$^+$], 298 (100) [M+Na$^+$], 276 (74) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{14}H_{14}NO_3S$, [M+H$^+$] 276.0689, found 276.0688.
The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 2-Methyl-*N*-tosylbenzamide (135b)



The general procedure **B** was followed using 2-methylbenzoyl chloride (2.72 g, 17.6 mmol, 1.1 equiv) in PhMe (14 mL), *p*-toluene sulfonamide (2.91 g, 16.0 mmol, 1.0 equiv), NEt_3 (4.05 g, 40.0 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (32 mL). Recrystallization from EtOH yielded **135b** (2.11 g, 46%) as a colorless solid.

M.r.: 113−115 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.02 (brs, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 8.1, 1.4 Hz, 1H), 7.32 (dd, J = 7.6, 1.3 Hz, 3H), 7.15 (dd, J = 7.0, 7.0 Hz, 2H), 2.43 (s, 3H), 2.32 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.5 (C_q), 145.2 (C_q), 138.0 (C_q), 135.7 (C_q), 132.2 (C_q), 131.8 (CH), 131.7 (CH), 129.7 (CH), 128.6 (CH), 127.5 (CH), 126.0 (CH), 21.8 (CH_3), 20.1 (CH_3).

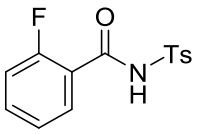
IR (neat): 3259, 1711, 1595, 1409, 1335, 1291, 1242, 1182, 1165, 1119 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 328 (9) [M+K$^+$], 312 (100) [M+Na$^+$], 290 (78) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{16}NO_3S$, [M+H$^+$] 290.0845, found 290.0848.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 2-Fluoro-*N*-tosylbenzamide (135c)



The general procedure **B** was followed using oxalylchloride (4.55 g, 45.0 mmol, 1.2 equiv) and 2-fluorobenzoic acid (5.24 g, 37.4 mmol, 1.1 equiv) in PhMe (30 mL). The crude product, 2-fluorobenzoyl chloride (5.93 g, 37.4 mmol, 1.1 equiv) in PhMe (30 mL) was added to a solution of *p*-toluene sulfonamide (5.82 g, 34.0 mmol, 1.0 equiv), NEt_3 (8.10 g, 80.0 mmol, 2.5 equiv) and DMAP (2 mg, 0.016 mmol, 0.5 mol %) in EtOAc (68 mL). Recrystallization from EtOH yielded **135c** (7.52 g, 78%) as a colorless solid.

M.r.: 134−135 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.02 (d, J = 14.9 Hz, 1H), 8.09–7.98 (m, 2H), 7.95 (dd, J = 7.9, 1.9 Hz, 1H), 7.53 (dddd, J = 8.4, 7.9, 5.3, 1.9 Hz, 1H), 7.38–7.29 (m, 2H), 7.26–7.19 (m, 1H), 7.13 (ddd, J = 12.3, 8.4, 1.1 Hz, 1H), 2.41 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 160.8 ($^1J_{C\text{-}F}$ = 249.0 Hz, C_q), 160.2 ($^3J_{C\text{-}F}$ = 3.0 Hz, C_q), 145.4 (C_q), 135.7 ($^3J_{C\text{-}F}$ = 9.7 Hz, CH), 135.5 (C_q), 132.2 ($^4J_{C\text{-}F}$ = 1.2 Hz, CH), 129.7 (CH), 128.9 (CH), 125.2 ($^3J_{C\text{-}F}$ = 3.2 Hz, CH), 118.5 ($^3J_{C\text{-}F}$ = 10.4 Hz, C_q), 116.3 ($^2J_{C\text{-}F}$ = 24.6 Hz, CH), 21.6 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -104.7– -115.1 (m).

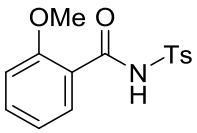
IR (neat): 3324, 1701, 1613, 1595, 1454, 1426, 1345, 1279, 1209, 1186 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 316 (100) [M+Na$^+$], 294 (68) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{13}FNO_3S$, [M+H$^+$] 294.0595, found 294.0597.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 4-Methoxy-*N*-tosylbenzamide (135d)



The general procedure **B** was followed using oxalylchloride (4.27 g, 42.2 mmol, 1.2 equiv) and 2-methoxybenzoic acid (5.35 g, 35.2 mmol, 1.1 equiv) in PhMe (28 mL). The crude product, 2-methoxybenzoyl chloride (6.01 g, 35.2 mmol, 1.1 equiv) in PhMe (28 mL) was added to a solution of *p*-toluene sulfonamide (5.44 g, 32.0 mmol, 1.0 equiv), NEt_3 (8.10 g, 80.0 mmol, 2.5 equiv) and DMAP (2 mg, 0.016 mmol, 0.5 mol %) in EtOAc (64 mL). Recrystallization from EtOH yielded **135d** (7.52 g, 78%) as a colorless solid.

M.r.: 128−130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.36 (brs, 1H), 8.17–7.98 (m, 3H), 7.52 (ddd, J = 8.5, 7.3, 1.9 Hz, 1H), 7.37–7.32 (m, 2H), 7.10–6.95 (m, 2H), 4.05 (s, 3H), 2.42 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.4 (C_q), 157.9 (C_q), 144.9 (C_q), 136.2 (C_q), 135.2 (CH), 132.9 (CH), 129.6 (CH), 128.8 (CH), 121.9 (CH), 119.0 (C_q), 111.8 (CH), 56.6 (CH_3), 21.7 (CH_3).

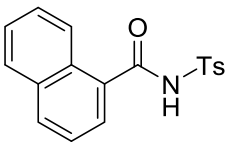
IR (neat): 3272, 1676, 1598, 1443, 1410, 1339, 1288, 1245, 1213, 1161 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 344 (7) [M+K^+], 328 (100) [M+Na^+], 306 (68) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{16}NO_4S$, [M+H^+] 306.0795, found 306.0795.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of *N*-Tosyl-1-naphtamide (135e)



The general procedure **B** was followed using oxalylchloride (3.06 g, 24.1 mmol, 1.2 equiv) and 1-naphthoic acid (3.46 g, 20.1 mmol, 1.1 equiv) in PhMe (16 mL). The crude product, 1-naphthoyl chloride (3.83 g, 20.1 mmol, 1.1 equiv) in PhMe (16 mL) was added to a solution of *p*-toluene sulfonamide (3.11 g, 18.3 mmol, 1.0 equiv), NEt_3 (4.62 g, 45.8 mmol, 2.5 equiv) and DMAP (1 mg, 0.009 mmol, 0.5 mol %) in EtOAc (37 mL). Recrystallization from EtOH yielded **135e** (4.34 g, 73%) as a colorless solid.

M.p.: 143 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.70 (brs, 1H), 8.23–8.14 (m, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.96 (ddd, J = 8.5, 7.3, 1.0 Hz, 1H), 7.89–7.80 (m, 1H), 7.67 (dd, J = 7.2, 1.2 Hz, 1H), 7.57–7.42 (m, 2H), 7.42–7.35 (m, 3H), 2.47 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.0 (C_q), 145.4 (C_q), 135.6 (C_q), 133.9 (CH), 133.0 (C_q), 130.2 (C_q), 130.1 (C_q), 129.8 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.0 (CH), 126.6 (CH), 125.0 (CH), 124.5 (CH), 21.9 (CH_3).

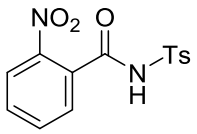
IR (neat): 3257, 3161, 1678, 1594, 1510, 1412, 1341, 1240, 1182, 1160 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 348 (100) [M+Na$^+$], 326 (64) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{16}NO_3S$, [M+H$^+$] 326.0845, found 326.0843.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 2-Nitro-*N*-tosylbenzamide (135f)



The general procedure **B** was followed using oxalylchloride (2.14 g, 21.1 mmol, 1.2 equiv) and 2-nitrobenzoic acid (2.94 g, 17.6 mmol, 1.1 equiv) in PhMe (30 mL). The crude product, 2-nitrobenzoyl chloride (3.27 g, 17.6 mmol, 1.1 equiv) in PhMe (14 mL) was added to a solution of *p*-toluene sulfonamide (2.91 g, 16.0 mmol, 1.0 equiv), NEt_3 (4.05 g, 40.0 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (32 mL). Recrystallization from EtOH yielded **135f** (4.14 g, 76%) as a colorless solid.

M.p.: 121 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.18 (brs, 1H), 8.03 (dd, J = 8.2, 1.3 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.68 (dd, J = 7.6, 1.3 Hz, 1H), 7.63–7.54 (m, 1H), 7.50 (dd, J = 7.4, 1.6 Hz, 1H), 7.42–7.26 (m, 2H), 2.46 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.1 (C_q), 145.7 (C_q), 145.5 (C_q), 134.6 (C_q), 134.4 (CH), 131.6 (CH), 130.1 (C_q), 129.8 (CH), 128.9 (CH), 128.9 (CH), 124.7 (CH), 21.9 (CH_3).

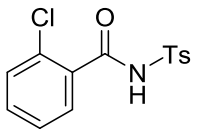
IR (neat): 3214, 3071, 2853, 1708, 1596, 1449, 1350, 1172, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 343 (100) [M+Na$^+$], 321 (16) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{13}N_2O_5S$, [M+H$^+$] 321.0540, found 321.0537.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 2-Chloro-*N*-tosylbenzamide (135g)



The general procedure **B** was followed using 2-chlorobenzoyl chloride (2.76 g, 17.6 mmol, 1.1 equiv) PhMe (14 mL), *p*-toluene sulfonamide (2.91 g, 16.0 mmol, 1.0 equiv), NEt_3 (4.05 g, 40.0 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (32 mL). Recrystallization from EtOH yielded **135g** (3.14 g, 64%) as a colorless solid.

M.r.: 125−126 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.90 (brs, 1H), 8.15–7.84 (m, 2H), 7.80–7.58 (m, 1H), 7.55–7.27 (m, 5H), 2.45 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.2 (C_q), 145.5 (C_q), 135.3 (C_q), 133.3 (CH), 131.6 (C_q), 131.3 (CH), 131.0 (C_q), 130.8 (CH), 129.8 (CH), 128.9 (CH), 127.6 (CH), 21.9 (CH_3).

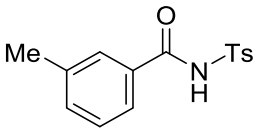
IR (neat): 3208, 1704, 1592, 1436, 1342, 1315, 1277, 1232, 1155, 1105 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 348 (12) [M+K^+], 332 (100) [M+Na^+], 310 (68) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{14}H_{13}ClNO_3S$, [M+H^+] 310.0299, found 310.0299.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 3-Methyl-*N*-tosylbenzamide (135h)



The general procedure **B** was followed using 3-methylbenzoyl chloride (2.72 g, 17.6 mmol, 1.1 equiv) in PhMe (14 mL), *p*-toluene sulfonamide (2.91 g, 16.0 mmol, 1.0 equiv), triethylamine (4.05 g, 40.0 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (32 mL). Recrystallization from EtOH yielded **135h** (3.77 g, 81%) as a colorless solid.

M.r.: 115−118 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.77 (brs, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.72–7.53 (m, 2H), 7.51–7.34 (m, 2H), 7.34–7.11 (m, 2H), 2.40 (s, 3H), 2.32 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.4 (C_q), 145.3 (C_q), 139.1 (C_q), 135.7 (C_q), 134.4 (CH), 131.3 (C_q), 129.7 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 124.9 (CH), 21.8 (CH_3), 21.1 (CH_3).

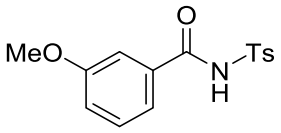
IR (neat): 3293, 1695, 1595, 1433, 1393, 1338, 1302, 1260, 1192, 1180 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 328 (5) [M+K^+], 312 (100) [M+Na^+], 290 (55) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{16}NO_3S$, [M+H^+] 290.0845, found 290.0847.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 3-Methoxy-*N*-tosylbenzamide (135i)



The general procedure **B** was followed using 3-methoxybenzoyl chloride (3.00 g, 17.6 mmol, 1.1 equiv) in PhMe (14 mL), *p*-toluene sulfonamide (2.91 g, 16.0 mmol, 1.0 equiv), NEt_3 (4.05 g, 40.0 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (32 mL). Recrystallization from EtOH yielded **135i** (4.26 g, 79%) as a colorless solid.

M.r.: 115−118 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.60 (brs, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.52–7.18 (m, 5H), 7.13–7.05 (m, 1H), 3.76 (s, 3H), 2.43 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.5 (C_q), 160.0 (C_q), 145.4 (C_q), 135.5 (C_q), 132.5 (C_q), 130.0 (CH), 129.7 (CH), 128.7 (CH), 120.5 (CH), 120.1 (CH), 112.2 (CH), 55.4 (CH_3), 21.6 (CH_3).

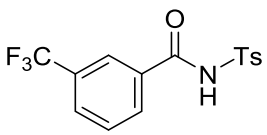
IR (neat): 3261, 1698, 1585, 1455, 1439, 1401, 1337, 1292, 1268, 1210 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 344 (11) [M+K^+], 328 (100) [M+Na^+], 306 (84) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{16}NO_4S$, [M+H^+] 306.0795, found 306.0792.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of *N*-Tosyl-3-(trifluoromethyl)benzamide (135j)



The general procedure **B** was followed using oxalylchloride (3.06 g, 24.1 mmol, 1.2 equiv) and 3-(trifluoromethyl)bencoic acid (3.82 g, 20.1 mmol, 1.1 equiv) in PhMe (16 mL). The crude product, 1-naphthoyl chloride (4.19 g, 20.1 mmol, 1.1 equiv) in PhMe (16 mL) was added to a solution of *p*-toluene sulfonamide (3.11 g, 18.3 mmol, 1.0 equiv), NEt_3 (4.62 g, 45.8 mmol, 2.5 equiv) and DMAP (1 mg, 0.009 mmol, 0.5 mol %) in EtOAc (40 mL). Recrystallization from EtOH yielded **135j** (6.14 g, 89%) as a colorless solid.

M.r.: 162−163 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.98 (brs, 1H), 8.15 (s, 1H), 8.10–8.01 (m, 3H), 7.77 (dd, J = 7.9, 0.9 Hz, 1H), 7.55 (dd, J = 7.9, 0.8 Hz, 1H), 7.34 (dd, J = 8.5, 0.9 Hz, 2H), 2.43 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 163.6 (C_q), 145.7 (C_q), 135.2 (C_q), 132.1 (C_q), 131.5 ($^2J_{C\text{-}F}$ = 33.2 Hz, C_q), 131.2 (CH), 130.0 ($^3J_{C\text{-}F}$ = 3.7 Hz, CH), 129.8 (CH), 129.7 (CH), 128.7 (CH), 123.3 ($^1J_{C\text{-}F}$ = 273.0 Hz, CH), 97.1 (C_q), 21.8 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -63.0 (s).

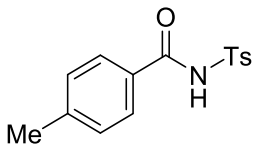
IR (neat): 3298, 1699, 1594, 1424, 1346, 1328, 1239, 1158, 1127, 1059 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 366 (100) [M+Na^+], 344 (46) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{15}H_{13}F_3NO_3S$, [M+H^+] 344.0563, found 344.0556.

The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 4-Methyl-*N*-tosylbenzamide (135k)



The general procedure **B** was followed using 4-methylbenzoyl chloride (2.72 g, 17.6 mmol, 1.1 equiv) in PhMe (14 mL), *p*-toluene sulfonamide (2.91 g, 16.0 mmol, 1.0 equiv), NEt_3 (4.05 g, 40.0 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (32 mL). Recrystallization from EtOH yielded **135k** (3.56 g, 70%) as a colorless solid.

M.r.: 127−129 °C.

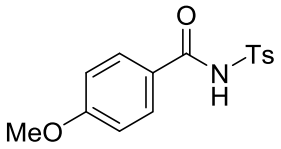
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.19 (brs, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H), 2.39 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.1 (C_q), 144.1 (C_q), 143.5 (C_q), 136.7 (C_q), 129.4 (CH), 129.0 (CH), 128.7 (C_q), 128.3 (CH), 127.6 (CH), 20.9 (CH_3), 20.9 (CH_3).

IR (neat): 3295, 1774, 1696, 1609, 1420, 1333, 1298, 1254, 1165, 1067 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 312 (82) [M+Na$^+$], 290 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{15}H_{16}NO_3S$, [M+H$^+$] 290.0845, found 290.0847.
The spectral data are in accordance with those reported in the literature.[114]

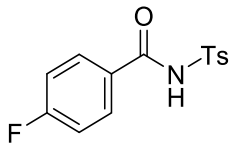
Synthesis of 4-Methoxy-*N*-tosylbenzamide (135l)



The general procedure **B** was followed using 4-methoxybenzoyl chloride (2.80 g, 16.4 mmol, 1.1 equiv) in PhMe (13 mL), *p*-toluene sulfonamide (2.59 g, 15.0 mmol, 1.0 equiv), NEt_3 (3.78 g, 37.4 mmol, 2.5 equiv) and DMAP (1 mg, 0.008 mmol, 0.5 mol %) in EtOAc (30 mL). Recrystallization from EtOH yielded **135l** (2.35 g, 52%) as a colorless solid.

M.r.: 152−154 °C.
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.19 (brs, 1H), 8.09–7.63 (m, 4H) 7.53–7.30 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 2.38 (s, 3H).
^{13}C-NMR (125 MHz, DMSO-d_6): δ = 165.1 (C_q), 162.8 (C_q), 143.3 (C_q), 137.7 (C_q), 130.4 (CH), 129.2 (CH), 127.5 (CH), 124.6 (C_q), 113.6 (CH), 55.4 (CH_3), 20.9 (CH_3).
IR (neat): 3230, 1742, 1667, 1603, 1520, 1437, 1417, 1340, 1317, 1254 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 344 (9) [M+K$^+$], 328 (100) [M+Na$^+$], 306 (77) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{15}H_{16}NO_4S$, [M+H$^+$] 306.0795, found 306.0796.
The spectral data are in accordance with those reported in the literature.[114]

Synthesis of 4-Fluoro-*N*-tosylbenzamide (135m)



The general procedure **B** was followed using oxalylchloride (4.55 g, 45.0 mmol, 1.2 equiv) and 4-fluorobenzoic acid (5.24 g, 37.4 mmol, 1.1 equiv) in PhMe (30 mL). The crude product, 2-fluorobenzoyl chloride (5.93 g, 37.4 mmol, 1.1 equiv) in PhMe (30 mL) was added to a solution of *p*-toluene sulfonamide (5.82 g, 34.0 mmol, 1.0 equiv), NEt_3 (8.10 g, 80.0 mmol, 2.5 equiv) and DMAP (2 mg, 0.016 mmol, 0.5 mol %) in EtOAc (68 mL). Recrystallization from EtOH yielded **135m** (7.52 g, 69%) as a colorless solid.

M.p.: 160 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.78 (s 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.87 (dd, J = 8.8, 5.1 Hz, 2H), 7.42–7.15 (m, 2H), 7.04 (d, J = 8.6 Hz, 2H) 2.41 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.9 ($^{1}J_{C\text{-}F}$ = 255.5 Hz, C_q), 163.7 (C_q), 145.5 (C_q), 135.4 (C_q), 130.8 ($^{3}J_{C\text{-}F}$ = 9.4 Hz, CH), 129.8 (CH), 128.7 (CH), 127.4 ($^{4}J_{C\text{-}F}$ = 3.0 Hz, C_q), 116.1 ($^{2}J_{C\text{-}F}$ = 22.2 Hz, CH), 21.6 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -111.8 (dddd, J = 14.4, 12.9, 7.9, 5.4 Hz).

IR (neat): 3086, 2879, 2858, 1678, 1599, 1508, 1439, 1347, 1305, 1259 cm^{-1}.

MS (ESI) *m/z* (relative intensity):332 (7) [M+K^+], 316 (100) [M+Na^+], 294 (50) [M+H^+].

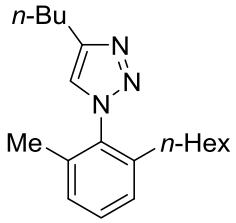
HR-MS (ESI) *m/z* calcd for $C_{14}H_{13}FNO_3S$, [M+H^+] 294.0595, found 294.0594.

The spectral data are in accordance with those reported in the literature.[114]

5.3.3 Synthesis of Alkylated *N*-Aryl-1,2,3-triazoles

Synthesis of 4-*n*-Butyl-1-(2-*n*-hexyl-6-methylphenyl)-1*H*-1,2,3-triazole (133aa) and 4-*n*-Butyl-1-[2-methyl-6-(3-methylbenzyl)phenyl]-1*H*-1,2,3-triazole (138a)

The general procedure **C** was followed using 4-*n*-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), 1-bromo-*n*-hexane (**40a**) (495.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %) in *m*-xylene. Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133aa** (60 mg, 20%) and **138a** (16 mg, 5%) as colorless oils.



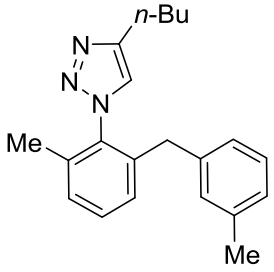
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.17 (ddd, *J* = 8.5, 7.3, 1.0 Hz, 2H), 2.92–2.70 (m, 2H), 2.37–2.08 (m, 2H), 1.97 (s, 3H), 1.74 (ddt, *J* = 8.6, 7.5, 6.4 Hz, 2H), 1.51–1.34 (m, 4H), 1.29–1.07 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 140.4 (C_q), 135.8 (C_q), 135.7 (C_q), 130.0 (CH), 128.4 (CH), 127.6 (CH), 122.9 (CH), 31.7 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 14.4 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2926, 2857, 1599, 1550, 1482, 1466, 1410, 1378, 1229 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 322 (8) $[M+Na^+]$, 300 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd. for $C_{19}H_{30}N_3$, $[M+H^+]$ 300.2434, found 300.2435.



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.24–7.14 (m, 2H), 7.09 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.04–7.02 (m, 2H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.82–6.63 (m, 2H), 3.62 (s,

2H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.26 (s, 3H), 1.97 (s, 3H), 1.74–1.57 (m, 2H), 1.48–1.31 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 147.9 (C_q), 139.6 (C_q), 138.6 (C_q), 138.0 (C_q), 136.0 (C_q), 135.9 (C_q), 130.0 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 127.0 (CH), 125.8 (CH), 123.1 (CH), 37.4 (CH_2), 31.7 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 17.6 (CH_3), 14.1 (CH_3).

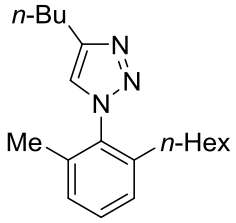
IR (ATR): $\tilde{\nu}$ = 3134, 2956, 2928, 2860, 1608, 1561, 1462, 1434, 1409, 1320 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 342 (64) [M+Na$^+$], 320 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd. for $C_{21}H_{26}N_3$, [M+H$^+$] 320.2121, found 320.2123.

Synthesis of 4-*n*-Butyl-1-(2-*n*-hexyl-6-methylphenyl)-1*H*-1,2,3-triazole (133aa) and 1-(2-*n*-Benzyl-6-methylphenyl)-4-butyl-1*H*-1,2,3-triazole (138b)

The general procedure **C** was followed using 4-*n*-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), 1-bromo-*n*-hexane (**40a**) (495.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133aa** (127 mg, 42%) and **138b** (49 mg, 16%) as colorless oils.



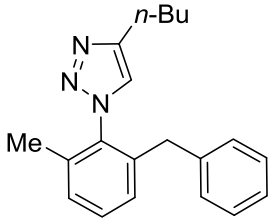
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 2.92–2.70 (m, 2H), 2.37–2.08 (m, 2H), 1.97 (s, 3H), 1.74 (ddt, *J* = 8.6, 7.5, 6.4 Hz, 2H), 1.51–1.34 (m, 4H), 1.29–1.07 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 140.4 (C_q), 135.8 (C_q), 135.7 (C_q), 130.0 (CH), 128.4 (CH), 127.6 (CH), 122.9 (CH), 31.7 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 14.4 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 2926, 2857, 1599, 1550, 1482, 1466, 1410, 1378, 1229 cm^{-1}.

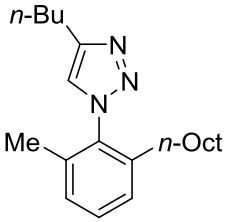
MS (ESI) *m/z* (relative intensity): 322 (8) [M+Na$^+$], 300 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd. for $C_{19}H_{30}N_3$, [M+H$^+$] 300.2434, found 300.2435.



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.19 (ddd, *J* = 8.6, 7.4, 1.7 Hz, 5H), 7.00 (s, 1H), 6.98–6.87 (m, 2H), 3.67 (s, 2H), 2.86–2.62 (m, 2H), 1.97 (s, 3H), 1.72–1.56 (m, 2H), 1.49–1.28 (m, 2H), 1.08–0.81 (m, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.0 (C_q), 139.7 (C_q), 138.6 (C_q), 136.1 (C_q), 136.0 (C_q), 130.0 (CH), 129.1 (CH), 128.7 (CH), 128.7 (CH), 128.4 (CH), 126.3 (CH), 123.0 (CH), 37.5 (CH_2), 31.7 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 17.6 (CH_3), 14.1 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3136, 3027, 2956, 2928, 2859, 1583, 1483, 1454, 1322, 1211 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 328 (69) [M+Na$^+$], 306 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{20}H_{24}N_3$, [M+H$^+$] 306.1965, found 306.1957.

Synthesis of 4-*n*-Butyl-1-(2-methyl-6-*n*-octylphenyl)-1*H*-1,2,3-triazole (133ab)

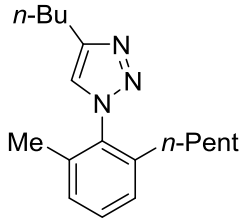


The general procedure **C** was followed using 4-*n*-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), 1-bromo-*n*-octane (**40b**) (579.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133ab** (136 mg, 41%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.21–7.05 (m, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.35–2.10 (m, 2H), 1.97 (s, 3H), 1.81–1.65 (m, 2H), 1.54–1.33 (m, 4H), 1.32–1.06 (m, 10H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 140.4 (C_q), 135.8 (C_q), 135.7 (C_q), 130.0 (CH), 128.4 (CH), 127.6 (CH), 122.9 (CH), 32.0 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 14.2 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2954, 2923, 2855, 1600, 1550, 1482, 1466, 1410, 1378, 1210 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 350 (2) [M+Na$^+$], 328 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{21}H_{34}N_3$, [M+H$^+$] 328.2747, found 328.2751.

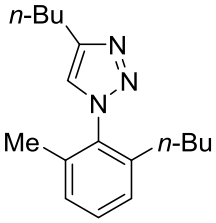
Synthesis of 4-*n*-Butyl-1-(2-methyl-6-*n*-pentylphenyl)-1*H*-1,2,3-triazole (133ac)



The general procedure **C** was followed using 4-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), 1-bromo-*n*-pentane (**40c**) (453.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133ac** (104 mg, 37%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.22–7.12 (m, 2H), 2.96–2.69 (m, 2H), 2.30–2.12 (m, 2H), 1.97 (s, 3H), 1.86–1.66 (m, 2H), 1.51–1.35 (m, 4H), 1.25–1.05 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 140.4 (C_q), 135.9 (C_q), 135.7 (C_q), 130.0 (CH), 128.4 (CH), 127.6 (CH), 122.9 (CH), 31.7 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 30.9 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 14.0 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2954, 2927, 2859, 1551, 1482, 1410, 1210, 1169, 1107, 1038 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 308 (7) [M+Na$^+$], 286 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{18}H_{28}N_3$, [M+H$^+$] 286.2278, found 286.2281.

Synthesis of 4-*n*-Butyl-1-(2-*n*-butyl-6-methylphenyl)-1*H*-1,2,3-triazole (133ad)

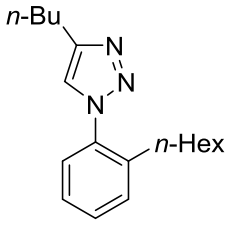


The general procedure **C** was followed using 4-*n*-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), 1-bromo-*n*-butane (**40a**) (411.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate

(68.9 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133ad** (108 mg, 42%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H). 7.21–7.12 (m, 2H), 2.92–2.74 (m, 2H), 2.30–2.14 (m, 2H), 1.96 (s, 3H), 1.73 (ddt, *J* = 8.5, 7.4, 6.4 Hz, 2H), 1.51–1.26 (m, 4H), 1.31–1.05 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 140.4 (C_q), 135.9 (C_q), 135.7 (C_q), 129.9 (CH), 128.3 (CH), 127.6 (CH), 122.9 (CH), 33.3 (CH_2), 31.7 (CH_2), 31.9 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 22.3 (CH_3), 17.5 (CH_3), 13.9 (CH_3), 13.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2955, 2929, 2860, 1550, 1482, 1467, 1379, 1208, 1170, 1106 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 294 (6) [M+Na$^+$], 272 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{17}H_{26}N_3$, [M+H$^+$] 272.2121, found 272.2124.

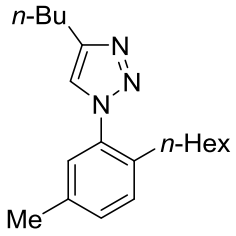
Synthesis of 4-*n*-Butyl-1-(2-*n*-hexylphenyl)-1*H*-1,2,3-triazole (133ba)



The general procedure **C** was followed using 4-*n*-Butyl-1-phenyl-1*H*-1,2,3-triazole (**123b**) (201.0 mg, 1.00 mmol), 1-bromo-*n*-hexane (**40a**) (495.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133ba** (111 mg, 39%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1H), 7.43–7.31 (m, 2H), 7.31–7.27 (m, 2H), 2.90–2.72 (m, 2H), 2.56–2.34 (m, 2H), 1.73 (ddt, *J* = 8.7, 7.6, 6.4 Hz, 2H), 1.54–1.36 (m, 4H), 1.31–1.08 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.2 (C_q), 139.0 (C_q), 136.5 (C_q), 130.6 (CH), 129.9 (CH), 126.7 (CH), 126.5 (CH), 122.7 (CH), 33.3 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 29.2 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3149, 2956, 2934, 2871, 1704, 1639, 1582, 1497, 1365, 1320 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 308 (5) [M+Na$^+$], 286 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{18}H_{28}N_3$, [M+H$^+$] 286.2278, found 286.2277.

Synthesis of 4-*n*-Butyl-1-(2-*n*-hexyl-5-metylphenyl)-1*H*-1,2,3-triazole (133ca)

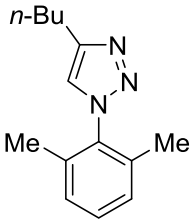


The general procedure **C** was followed using 4-*n*-Butyl-1-(*m*-tolyl)-1*H*-1,2,3-triazole (**123c**) (215.0 mg, 1.00 mmol), 1-bromo-*n*-hexane (**40a**) (495.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **133ca** (75 mg, 25%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.25–7.15 (m, 2H), 7.10 (dt, J = 1.6, 0.8 Hz, 1H), 2.92–2.67 (m, 2H), 2.50–2.36 (m, 2H), 2.35 (s, 3H), 1.81–1.61 (m, 2H), 1.52–1.30 (m, 4H), 1.19 (dddd, J = 9.2, 7.1, 5.5, 2.1 Hz, 6H), 0.96 (t, J = 7.3 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.1 (C_q), 136.7 (C_q), 136.3 (C_q), 135.7 (C_q), 130.6 (CH), 130.3 (CH), 127.0 (CH), 122.6 (CH), 31.7 (CH_2), 31.6 (CH_2), 30.9 (CH_2), 30.9 (CH_2), 29.1 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 20.8 (CH_3), 14.1 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2954, 2924, 2857, 1619, 1579, 1551, 1210, 1459, 1378, 1211 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 322 (10) [M+Na$^+$], 300 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{19}H_{30}N_3$, [M+H$^+$] 300.2434, found 300.2433.

5.3.4 Synthesis of Methylated *N*-Aryl-1,2,3-triazoles

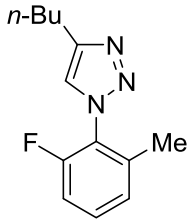
Synthesis of 4-*n*-Butyl-1-(2,6-dimethylphenyl)-1*H*-1,2,3-triazole (139aa)



The general procedure **D** was followed using 4-*n*-Butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), methyl iodide (**41a**) (442.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %) in PhMe (4 mL). Purification by column chromatography (*n*-pentane/EtOAc 19/1 → 9/1) yielded **139a** (138 mg, 60%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 7.32–7.23 (m, 1H), 7.18–7.08 (m, 2H) 2.94–2.64 (m, 2H), 1.98 (s, 6H), 1.84–1.62 (m, 2H), 1.42 (dq, J = 14.5, 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 148.3 (C_q), 136.3 (C_q), 135.6 (C_q), 129.9 (CH), 128.4 (CH), 122.4 (CH), 31.6 (CH_2), 25.5 (CH_2), 22.4 (CH_2), 17.4 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3131, 2955, 2927, 2859, 1550, 1486, 1379, 1212, 1179, 1095 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 252 (20) [M+Na$^+$], 230 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd. for $C_{14}H_{20}N_3$, [M+H$^+$] 230.1652, found 230.1647.

Synthesis of 4-*n*-Butyl-1-(2-fluoro-6-methylphenyl)-1*H*-1,2,3-triazole (139fa)



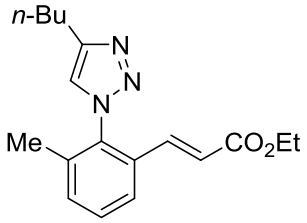
The general procedure **D** was followed using 4-*n*-butyl-1-(2-fluorophenyl)-1*H*-1,2,3-triazole (**123f**) (219.0 mg, 1.00 mmol), methyl iodide (**41a**) (442.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), K_2CO_3 (276.0 mg, 2.00 mmol) and potassium 4-(trifluormethyl)benzoate (68.9 mg, 30 mol %) in dioxane (4 mL). Purification by column

chromatography (*n*-pentane/EtOAc 19/1 → 9/1) yielded **139fa** (163 mg, 70%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1H), 7.41–7.34 (m, 1H), 7.17–7.05 (m, 2H), 2.89–2.77 (m, 2H), 2.17 (s, 3H), 1.81–1.69 (m, 2H), 1.51–1.36 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 157.0 ($^{1}J_{C\text{-}F}$ = 252.0 Hz, C_q), 148.2 (C_q), 137.9 (C_q), 130.8 ($^{3}J_{C\text{-}F}$ = 8.5 Hz, C_q), 131.1 ($^{3}J_{C\text{-}F}$ = 9.0 Hz, CH), 126.4 (CH), 126.4 (CH), 123.1 ($^{4}J_{C\text{-}F}$ = 1.5 Hz, CH), 113.9 ($^{2}J_{C\text{-}F}$ = 19.8 Hz, CH), 31.6 (CH_2), 25.5 (CH_2), 17.7 ($^{4}J_{C\text{-}F}$ = 2.4 Hz, CH_3), 14.1 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -122.7– -122.8 (m).
IR (ATR): $\tilde{\nu}$ = 2955, 2926, 2857, 1550, 1483, 1466, 1378, 1210, 1178, 1082 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 256 (5) [M+Na^+], 234 (100) [M+H^+].
HR-MS (ESI) *m/z* calcd. for $C_{13}H_{17}FN_3$, [M+H^+] 234.1401, found 234.1408.

5.3.5 Synthesis of Alkenylated *N*-Aryl-1,2,3-triazoles

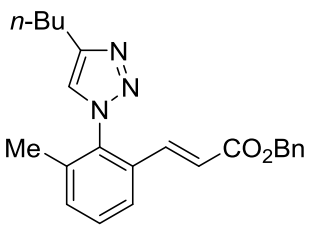
Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methylphenyl]acrylate (134ac)



The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 2/1) yielded **134ac** (247 mg, 82%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.39–7.34 (m, 2H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.23 (d, *J* = 16.0 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.03 (s, 3H), 1.86–1.66 (m, 2H), 1.51–1.31 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.1 (C_q), 148.8 (C_q), 138.3 (CH), 136.6 (C_q), 135.9 (C_q), 132.6 (C_q), 132.4 (CH), 130.3 (CH), 124.9 (CH), 123.4 (CH), 122.1 (CH), 60.7 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 14.3 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2931, 1710, 1479, 1236, 1166, 1037, 979, 787 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 352 (24) [M+K$^+$], 336 (24) [M+Na$^+$], 314 (100) [M+H$^+$], 240 (15), 216 (2).
HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}N_3O_2$, [M+H$^+$] 314.1863, found 314.1866.

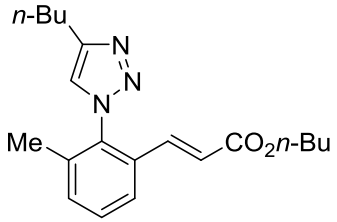
Synthesis of Benzyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methylphenyl]acrylate (134ad)



The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), benzyl acrylate (**17d**) (247.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 2/1) yielded **134ad** (255 mg, 68%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.6 Hz 1H), 7.43 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.38–7.28 (m, 7H), 7.06 (d, *J* = 16.0 Hz, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.15 (s, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.03 (s, 3H), 1.80–1.64 (m, 2H), 1.48–1.30 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.8 (C_q), 148.8 (C_q), 138.9 (CH), 136.6 (C_q), 135.9 (C_q), 135.9 (C_q), 132.6 (CH), 132.4 (C_q), 130.3 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 124.9 (CH), 123.3 (CH), 121.6 (CH), 66.5 (CH_2), 31.5 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 17.4 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2930, 1715, 1480, 1312, 1264, 1163, 1039, 697 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 414 (100) $[M+K^+]$, 398 (30) $[M+Na^+]$, 376 (66) $[M+H^+]$.
HR-MS (ESI) *m/z* calcd for $C_{23}H_{24}N_3O_2$, $[M+H^+]$ 376.2020, found 376.2023.

Synthesis of *n*-Butyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methylphenyl]acrylate (134ae)



The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (217.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 2/1) yielded **134ae** (229 mg, 67%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.3 Hz, 1H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.38–7.33 (m, 2H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 4.10 (t, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.03 (s, 3H), 1.82–1.70 (m, 2H), 1.65–1.53 (m, 2H), 1.50–1.26 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

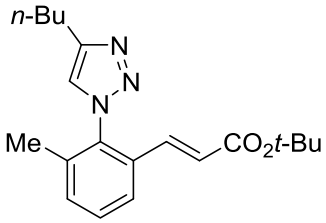
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.2 (C_q), 148.8 (C_q), 138.3 (CH), 136.7 (C_q), 135.9 (C_q), 132.6 (C_q), 132.5 (CH), 130.3 (CH), 124.9 (CH),123.3 (CH), 122.1 (CH), 64.7 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 19.3 (CH_2), 17.5 (CH_3), 13.9 (CH_3), 13.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2955, 1713, 1634, 1261, 1167, 1037, 817, 750 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 380 (100) [M+K^+], 364 (41) [M+Na^+], 342 (90) [M+H^+], 286 (3), 240 (7), 173 (3).

HR-MS (ESI) *m/z* calcd for $C_{20}H_{28}N_3O_2$, [M+H^+] 342.2176, found 342.2177.

Synthesis of *tert*-Butyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methylphenyl]acrylate (134af)



The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), *tert*-butyl acrylate (**17f**) (193.3 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 2/1) yielded **134af** (223 mg, 65%) as a colorless solid.

M.r.: 77–79 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.7 Hz, 1H), 7.46–7.30 (m, 3H), 6.89 (d, *J* = 16.0 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 1H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.02 (s, 3H), 1.87–1.65 (m, 2H), 1.50–1.36 (m, 2H), 1.43 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H).

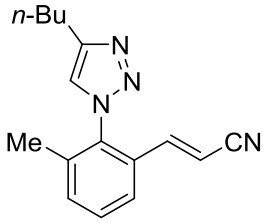
^{13}C-NMR (76 MHz, $CDCl_3$): δ = 165.4 (C_q), 148.7 (C_q), 137.3 (CH), 136.6 (C_q), 135.8 (C_q), 132.7 (C_q), 132.2 (CH), 130.2 (CH), 124.9 (CH), 123.9 (CH), 123.3 (CH), 80.9 (C_q), 31.7 (CH_2), 28.2 (CH_3), 25.4 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2956, 1712, 1637, 1498, 1367, 1179, 1038, 765 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 380 (100) [M+K^+], 364 (27) [M+Na^+], 342 (41) [M+H^+], 324 (8), 308 (10), 286 (86), 240 (5).

HR-MS (ESI) *m/z* calcd for $C_{20}H_{28}N_3O_2$, [M+H^+] 342.2176, found 342.2176.

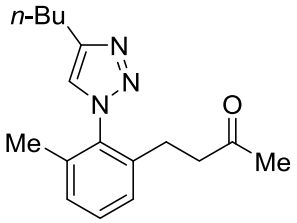
Synthesis of (*E*)-3-[2-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-3-methylphenyl]acrylonitrile (134ag)



The general procedure **E** was followed using 1-iodo-2-methylbenzene (**123a**) (215.0 mg, 1.00 mmol), acrylonitrile (**17g**) (98.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 3/1→1/1) yielded **134ag** (39 mg, 15%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.54–7.41 (m, 3H), 7.39 (s, 1H), 6.73 (d, *J* = 16.7 Hz, 1H), 5.75 (d, *J* = 16.7 Hz, 1H), 2.86 (t, *J* = 7.8 Hz, 2H), 2.04 (s, 3H), 1.77 (p, *J* = 7.6 Hz, 2H) 1.46 (dt, *J* = 14.8, 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 149.2 (C_q), 144.8 (CH), 137.0 (C_q), 135.5 (C_q), 133.5 (CH), 131.6 (C_q), 130.5 (CH), 124.2 (CH), 123.3 (CH), 117.4 (C_q), 100.1 (CH), 31.5 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 17.4 (CH_3), 14.0 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3135, 3060, 2956, 2928, 2860, 2219, 1620, 1586, 1549, 1478 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 289 (5) [M+Na$^+$], 267 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{16}H_{19}N_4$, [M+H$^+$] 267.1604, found 267.1607.

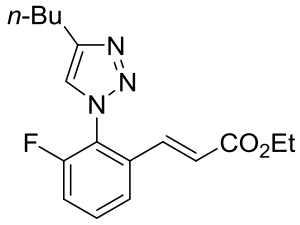
Synthesis of 4-[2-(4-*n*-Butyl-1*H*-1,2,3-triazol-1-yl)-3-methylphenyl]butan-2-on (141)



The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (215.0 mg, 1.00 mmol), methyl vinyl ketone (**17j**) (112.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.8 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 3/1 → 1/1) yielded **141** (186 mg, 65%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.39 (s, 1H), 7.37–7.29 (m, 1H), 7.18 (d, J = 7.7 Hz, 2H), 2.79 (d, J = 7.6 Hz, 2H), 2.64–2.56 (m, 2H), 2.54–2.42 (m, 2H), 2.03 (s, 3H), 1.97 (s, 3H), 1.80–1.67 (m, 2H), 1.50–1.48–1.32 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.4 (C_q), 148.5 (C_q), 138.7 (C_q), 136.0 (C_q), 136.0 (C_q), 130.2 (CH), 128.9 (CH), 127.8 (CH), 122.9 (CH), 44.8 (CH_2), 31.6 (CH_2), 29.9 (CH_3), 25.5 (CH_2), 25.5 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2929, 1714, 1483, 1363, 1214, 1163, 781, 417 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 324 (73) [M+K$^+$], 308 (35) [M+Na$^+$], 286 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{17}H_{24}N_3O$, [M+H$^+$] 286.1914, found 286.1920.

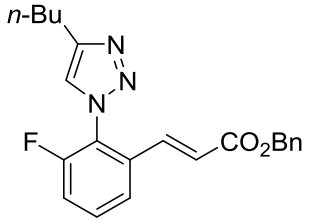
Synthesis of Ethyl (*E*)-3-[2-(4-*n*-Butyl-1*H*-1,2,3-triazol-1-yl)-3-fluorophenyl]acrylate (134fc)



The general procedure **E** was followed using 4-*n*-butyl-1-(2-fluorophenyl)-1*H*-1,2,3-triazole (**123f**) (219.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 7/1 → 2/1) yielded **134fc** (191 mg, 60%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.57–7.44 (m, 3H), 7.32–7.23 (m, 1H), 7.20 (d, J = 16.0 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.83 (d, J = 7.6 Hz, 2H), 1.80–1.67 (m, 2H), 1.53–1.34 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.8 (C_q), 158.7 ($^1J_{C\text{-}F}$ = 253 Hz, C_q), 148.7 (C_q), 137.1 ($^5J_{C\text{-}F}$ = 3 Hz, CH), 134.2 (C_q), 131.3 ($^2J_{C\text{-}F}$ = 9 Hz, CH), 124.7 ($^2J_{C\text{-}F}$ = 13 Hz, C_q), 123.8 ($^4J_{C\text{-}F}$ = 2 Hz, CH), 132.1 (CH), 123.0 ($^3J_{C\text{-}F}$ = 4 Hz, CH), 117.6 ($^2J_{C\text{-}F}$ = 20 Hz, CH), 60.9 (CH_2), 31.5 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).
^{19}F-NMR (283 MHz, $CDCl_3$): δ = -121.2– -121.3 (m).
IR (ATR): $\tilde{\nu}$ = 3149, 2934, 1705, 1639, 1365, 1321, 1255, 1192, 1039, 790 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 356 (25) [M+K$^+$], 340 (25) [M+Na$^+$], 318 (100) [M+H$^+$], 244 (10), 202 (1), 173 (3), 146 (1).
HR-MS (ESI) *m/z* calcd for $C_{17}H_{21}FN_3O_2$, [M+H$^+$] 318.1612, found 318.1623.

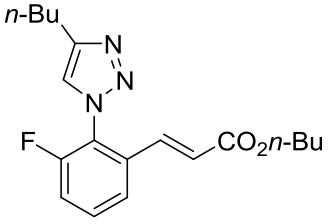
Synthesis of Benzyl (*E*)-3-[2-(4-*n*-Butyl-1*H*-1,2,3-triazol-1-yl)-4-fluorophenyl]acrylate (134fd)



The general procedure **E** was followed using 4-*n*-butyl-1-(2-fluorophenyl)-1*H*-1,2,3-triazole (**123f**) (219.0 mg, 1.00 mmol), benzyl acrylate (**17d**) (494.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134fd** (298 mg, 79%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.59–7.45 (m, 3H), 7.41–7.22 (m, 7H), 6.39 (d, J = 15.9 Hz, 1H), 5.18 (s, 2H), 2.83 (t, J = 7.8 Hz, 2H), 1.84–1.64 (m, 2H), 1.52–1.36 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ =165.6 (C_q), 157.0 ($^1J_{C\text{-}F}$ = 254 Hz, C_q), 148.7 (C_q), 137.9 ($^4J_{C\text{-}F}$ = 3 Hz, CH), 135.8 (C_q), 134.0 (C_q), 131.3 ($^3J_{C\text{-}F}$ = 8 Hz, CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 124.8 ($^2J_{C\text{-}F}$ = 13 Hz, C_q), 123.9 (CH), 123.0 ($^4J_{C\text{-}F}$ = 4 Hz, CH), 122.9 (CH), 117.7 ($^2J_{C\text{-}F}$ = 20 Hz, CH), 66.7 (CH_2), 31.4 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -121.2 (ddd, J = 9.7, 4.8, 1.5 Hz).
IR (ATR): $\tilde{\nu}$ = 2957, 1716, 1497, 1477, 1250, 1161, 1038, 797 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 418 (100) [M+K$^+$], 402 (15) [M+Na$^+$], 380 (28) [M+H$^+$], 217 (6), 169 (2) 152 (8), 108 (4).
HR-MS (ESI) *m/z* calcd for $C_{22}H_{23}FN_3O_2$, [M+H$^+$] 380.1769, found 380.1758.

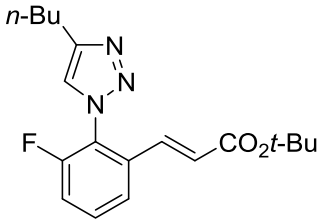
Synthesis of *n*-Butyl (*E*)-3-[2-(4-*n*-Butyl-1*H*-1,2,3-triazol-1-yl)-3-fluorophenyl]acrylate (134fe)



The general procedure **E** was followed using 4-*n*-butyl-1-(2-fluorophenyl)-1*H*-1,2,3-triazole (**123f**) (219.0 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (434.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134fe** (262 mg, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56–7.42 (m, 3H), 7.30–7.22 (m, 1H), 7.18 (d, *J* = 16.0 Hz, 1H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.11 (t, *J* = 6.7 Hz, 2H), 2.82 (t, *J* = 6.7 Hz, 2H) 1.78–1.69 (m, 2H), 1.63–1.53 (m, 2H), 1.47–1.38 (m, 2H), 1.37–1.27 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 165.8 (C_q), 157.0 ($^1J_{C\text{-}F}$ = 254 Hz, C_q), 148.7 (C_q), 137.2 ($^4J_{C\text{-}F}$ = 3 Hz, CH), 134.1 (C_q), 131.3 ($^3J_{C\text{-}F}$ = 9 Hz, CH), 124.7 ($^2J_{C\text{-}F}$ = 13 Hz, C_q), 123.8 ($^5J_{C\text{-}F}$ = 2 Hz, CH), 123.3 (CH), 123.0 ($^4J_{C\text{-}F}$ = 4 Hz, CH), 117.6 ($^2J_{C\text{-}F}$ = 20 Hz, CH), 64.8 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 19.2 (CH_2), 13.9 (CH_3), 13.8 (CH_3).
^{19}F-NMR (376 MHz, $CDCl_3$): *δ* = -121.2– -121.3 (m).
IR (ATR): $\tilde{\nu}$ = 2958, 1713, 1497, 1250, 1179, 1038, 795, 730 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 384 (100) [M+K$^+$], 368 (14) [M+Na$^+$], 346 (83) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{19}H_{25}FN_3O_2$, [M+H$^+$] 346.1925, found 346.1922.

Synthesis of *tert*-Butyl (*E*)-3-[1-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-fluorophenyl]acrylate (134ff)



The general procedure **E** was followed using 4-*n*-butyl-1-(2-fluorophenyl)-1*H*-1,2,3-triazole (**123f**) (219.0 mg, 1.00 mmol), *tert*-butyl acrylate (**17f**) (386.6 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (n-pentane/EtOAc 6/1) yielded **134ff** (193 mg, 56%) as a colorless solid.

M.r.: 85–86 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): *δ* = 7.58–7.43 (m, 3H), 7.32–7.21 (m, 1H), 7.10 (d, *J* = 15.9 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 2.84 (t, *J* = 7.8 Hz, 2H), 1.83–1.63 (m, 2H), 1.52–1.36 (m, 2H), 1.45 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.1 (C_q), 157.2 ($^1J_{C\text{-}F}$ = 254 Hz, C_q), 148.7 (C_q), 136.2 ($^4J_{C\text{-}F}$ = 3 Hz, CH), 134.4 (C_q), 131.3 ($^3J_{C\text{-}F}$ = 9 Hz, CH), 125.2 (CH), 124.8 ($^2J_{C\text{-}F}$ = 13 Hz, C_q), 123.9 (CH), 122.9 ($^4J_{C\text{-}F}$ = 4 Hz, CH), 117.4 ($^2J_{C\text{-}F}$ = 20 Hz, CH), 81.2 (C_q), 31.6 (CH_2), 28.2 (CH_3), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

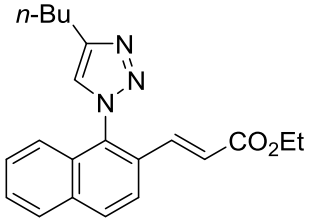
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -121.2– -121.4 (m).

IR (ATR): $\tilde{\nu}$ = 2956, 1697, 1475, 1289, 1230, 1156, 969, 806 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 384 (100) [M+K$^+$], 368 (21) [M+Na$^+$], 346 (21) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{24}FN_3O_2K$, [M+K$^+$] 384.1484, found 384.1474.

Synthesis of Ethyl (*E*)-3-[1-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)naphtalen-2-yl]acrylate (134hc)



The general procedure **E** was followed using 4-*n*-butyl-1-(naphtalen-2-yl)-1*H*-1,2,3-triazole (**123h**) (251.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (151.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 2/1) yielded **134hc** (203 mg, 58%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.62–7.50 (m, 2H), 7.48 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.18 (d, *J* = 16.0 Hz, 1H), 7.12 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.79 (t, *J* = 7.6 Hz, 2H), 1.87–1.74 (m, 2H) 1.56–1.36 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 3H).

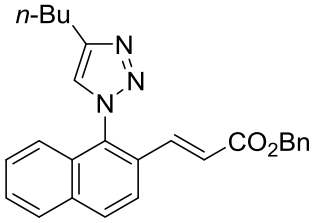
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.0 (C_q), 148.8 (C_q), 137.8 (CH), 134.4 (C_q), 133.3 (C_q), 130.8 (CH), 130.5 (C_q), 129.5 (C_q), 128.6 (CH), 128.1 (CH), 128.1 (CH), 124.8 (CH), 123.2 (CH), 122.7 (CH), 122.7 (CH), 60.8 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2931, 1712, 1635, 1292, 1262, 1178, 819, 751 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 388 (100) [M+K$^+$], 372 (30) [M+Na$^+$], 350 (88) [M+H$^+$], 324 (2), 276 (6).

HR-MS (ESI) *m/z* calcd for $C_{21}H_{24}N_3O_2$, [M+H$^+$] 350.1863, found 350.1867.

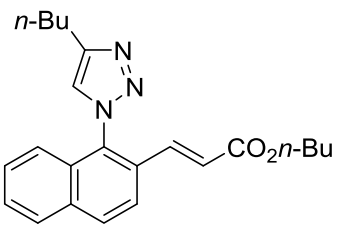
Synthesis of Benzyl (*E*)-3-[1-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)naphtalen-2-yl]acrylate (134hd)



The general procedure **E** was followed using 4-*n*-butyl-1-(naphthalene-1-yl)-1*H*-1,2,3-triazole (**123h**) (251.0 mg, 1.00 mmol), benzyl acrylate (**17d**) (494.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134hd** (287 mg, 70%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.65–7.52 (m, 2H), 7.52–7.45 (m, 1H), 7.41–7.30 (m, 5H), 7.25 (d, *J* = 16.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.19 (s, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.80 (ddt, *J* = 8.8, 7.6, 6.4 Hz, 2H), 1.56–1.40 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.8 (C_q), 148.8 (C_q), 138.4 (CH), 135.9 (C_q), 134.5 (C_q), 133.4 (C_q), 130.8 (CH), 130.5 (C_q), 129.4 (C_q), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 124.8 (CH), 123.2 (CH), 122.6 (CH), 122.2 (CH), 66.6 (CH_2), 31.5 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2929, 1712, 1634, 1261, 866, 734, 696 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 450 (100) [M+K$^+$], 434 (29) [M+Na$^+$], 412 (88) [M+H$^+$], 324 (2), 276 (6).
HR-MS (ESI) *m/z* calcd for $C_{26}H_{26}N_3O_2$, [M+H$^+$] 412.2020, found 412.2017.

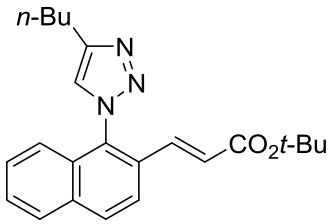
Synthesis of *n*-Butyl (*E*)-3-[1-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)naphtalen-2-yl]acrylate (134he)



The general procedure **E** was followed using 4-*n*-butyl-1-(naphthalene-1-yl)-1*H*-1,2,3-triazole (**123h**) (251.0 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (434.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134he** (268 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.59–7.43 (m, 2H), 7.49 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.19 (d, *J* = 16.0 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.91 (t, *J* = 6.6 Hz, 2H), 1.84–1.75 (m, 2H), 1.67–1.57 (m, 2H), 1.49 (h, *J* = 7.5 Hz, 2H), 1.42–1.28 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.2 (C_q), 148.8 (C_q), 137.8 (CH), 134.5 (C_q), 133.3 (C_q), 130.8 (CH), 130.6 (C_q), 129.6 (C_q), 128.6 (CH), 128.1 (CH), 128.1 (CH), 124.8 (CH), 123.3 (CH), 122.7 (CH), 122.7 (CH), 64.8 (CH_2), 31.7 (CH_2), 30.8 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 19.3 (CH_2), 13.9 (CH_3), 13.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2957, 1711, 1635, 1290, 1261, 1174, 978, 818 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 416 (100) $[M+K^+]$, 400 (16) $[M+Na^+]$, 378 (29) $[M+H^+]$, 290 (3), 252 (8), 232 (2), 217 (6), 169 (2) 152 (7), 102 (3).
HR-MS (ESI) *m/z* calcd for $C_{23}H_{28}N_3O_2$, $[M+H^+]$ 378.2176, found 378.2168.

Synthesis of *tert*-Butyl (*E*)-3-[1-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)naphtalen-2-yl]acrylate (134hf)



The general procedure **E** was followed using 4-*n*-butyl-1-(naphthalene-1-yl)-1*H*-1,2,3-triazole (**123h**) (251.0 mg, 1.00 mmol), *tert*-butyl acrylate (**17f**) (386.6 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 9/1) yielded **134hf** (271 mg, 72%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.68–7.46 (m, 3H), 7.17–7.04 (m, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 2.91 (t,

J = 6.7 Hz, 2H), 1.81 (p, *J* = 7.5 Hz, 2H), 1.56–1.38 (m, 2H), 1.47 (s, 9H), 1.00 (t, *J* = 7.3 Hz, 3H).

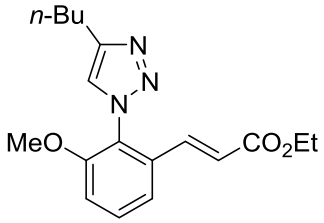
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.4 (C_q), 148.8 (C_q), 136.9 (CH), 134.4 (C_q), 133.2 (C_q), 130.7 (CH), 130.6 (C_q), 129.8 (C_q), 128.6 (CH), 128.0 (CH), 128.0 (CH), 124.8 (CH), 124.6 (CH), 123.3 (CH), 122.8 (CH), 81.1 (C_q), 31.8 (CH_2), 28.2 (CH_3), 25.5 (CH_2), 22.6 (CH_2), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2929, 1704, 1260, 1144, 979, 817, 751, 66 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 416 (100) [M+K$^+$], 378 (26) [M+H$^+$], 322 (13), 290 (3), 252 (9).

HR-MS (ESI) *m/z* calcd for $C_{23}H_{28}N_3O_2$, [M+H$^+$] 378.2176, found 378.2161.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methoxyphenyl]acrylate (134gc)



The general procedure **E** was followed using 4-*n*-butyl-1-(2-methoxyphenyl)-1*H*-1,2,3-triazole (**123c**) (231.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.8 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 3/1 → 1/1) yielded **134gc** (175 mg, 53%) as a colorless solid.

M.r.: 87-88 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 8.2, 8.2 Hz 1H), 7.39 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.09–6.98 (m, 2H), 6.24 (d, *J* = 16.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 2.80 (t, *J* = 7.6 Hz, 2H), 1.76–1.66 (m, 2H), 1.45–1.34 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).

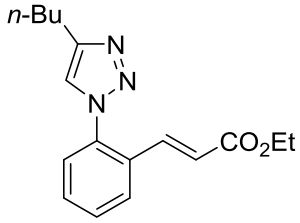
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.0 (C_q), 154.9 (C_q), 148.1 (C_q), 138.3 (CH), 133.6 (C_q), 131.0 (CH), 125.6 (C_q), 124.2 (CH), 122.3 (CH), 118.9 (CH), 113.1 (CH), 60.7 (CH_2), 56.3 (CH_3), 31.5 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.2 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2953, 1709, 1478, 1263, 1172, 1963, 1038, 800 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 368 (22) [M+K$^+$], 352 (21) [M+Na$^+$], 330 (100) [M+H$^+$], 318 (5), 256 (8), 241 (2).

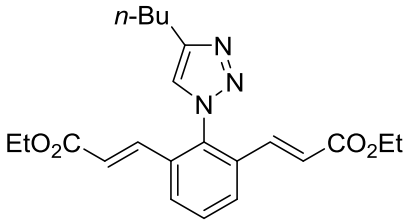
HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}N_3O_3$, [M+H$^+$] 330.1812, found 330.1818.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)phenyl]acrylate (134bc) and diethyl 3,3'-[2-(4-butyl-1*H*-1,2,3-triazol-1-yl)-1,3-phenylene](*2E, 2'E*)-diacrylate (142bc)



The general procedure **E** was followed using 4-*n*-butyl-1-phenyl-1*H*-1,2,3-triazole (**123b**) (100.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (199.6 mg, 1.00 mmol) and $AgSbF_6$ (51.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 9/1 → 2/1) yielded **134bc** (107 mg, 71%) and **142bc** (8 mg ,4%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.78–7.65 (m, 1H), 7.55–7.43 (m, 4H), 7.40 (d, *J* = 15.9 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 7.4 Hz, 2H), 1.81–1.65 (m, 2H), 1.52–1.34 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.1 (C_q), 148.8 (C_q), 138.6 (CH), 136.5 (C_q), 130.8 (CH), 130.4 (C_q), 129.9 (CH), 127.8 (CH), 126.6 (CH), 123.2 (CH), 122.2 (CH), 60.8 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2932, 1711, 1497, 1316, 1177, 1037, 764 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 338 (100) $[M+K^+]$, 322 (38) $[M+Na^+]$, 300 (81) $[M+H^+]$, 226 (14), 189 (1), 173 (3), 146 (2).
HR-MS (ESI) *m/z* calcd for $C_{17}H_{22}N_3O_2$, $[M+H^+]$ 300.1707, found 300.1708.



M.p.: 100 °C
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.9 Hz, 2H), 7.59 (ddt, *J* = 8.2, 7.5, 0.7 Hz, 1H), 7.43 (d, *J* = 0.8 Hz, 1H), 7.00 (d, *J* = 16.0 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 2.87 (ddd, *J* = 8.0, 7.3, 0.7 Hz, 2H), 1.85–1.67 (m, 2H), 1.49–1.41 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.97 (t, *J* = 7.4 Hz, 3H).

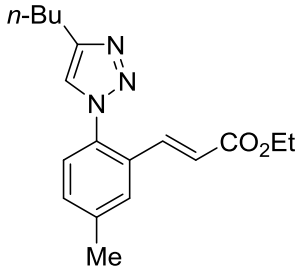
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.8 (C_q), 149.2 (C_q), 137.6 (CH), 135.3 (C_q), 133.5 (CH), 130.8 (CH), 128.6 (CH), 124.4 (CH), 123.2 (CH), 60.9 (CH_2), 31.7 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 14.0 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3121, 2961, 2929, 2852, 1595, 1552, 1499, 1466, 1413, 1323, 1244, 1223, 1075, 1040, 990, 913, 830, 758, 731, 683, 525, 480 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 436 (2) [M+K^+], 420 (13) [M+Na^+], 398 (100) [M+H^+], 324 (2), 300 (1).

HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_3O_4$, [M+H^+] 398.2074, found 398.2079.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-5-methylphenyl]acrylate (134ic) and Diethyl 3,3'-[2-(4-butyl-1*H*-1,2,3-triazol-1-yl)-5-methyl-1,3-phenylene](*2E, 2'E*)-diacrylate (142ic)



The general procedure **E** was followed using 4-*n*-butyl-1-(4-methylphenyl)-1*H*-1,2,3-triazole (**123i**) (215.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134ic** (175 mg, 56%) and **142ic** (15 mg, 7%) as colorless solids.

M.p.: 65 °C.

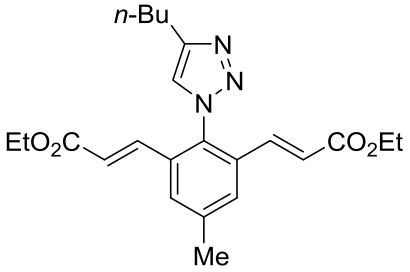
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.45 (s, 1H), 7.39–7.28 (m, 3H), 6.33 (d, *J* = 15.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 1.76–1.64 (m, 2H), 1.49–1.35 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.2 (C_q), 148.7 (C_q), 140.1 (C_q), 138.7 (CH), 134.3 (C_q), 131.5 (CH), 130.0 (C_q), 128.1 (CH), 126.5 (CH), 123.2 (CH), 121.9 (CH), 60.8 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 21.4 (CH_3), 14.3 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2926, 1708, 1503, 1366, 1257, 1226, 1034, 874, 559 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 352 (100) [M+K^+], 336 (36) [M+Na^+], 314 (72) [M+H^+], 240 (10), 173 (2).

HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}N_3O_2$, [M+H^+] 314.1863, found 314.1863.



M.r.: 58−60°C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 1.7 Hz, 2H), 7.93 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.46 (d, *J* = 0.8 Hz, 2H), 7.26 (d, *J* = 0.9 Hz, 2H), 2.79–2.52 (m, 10H), 1.57 (dt, *J* = 15.2, 7.9 Hz, 4H), 1.39–1.12 (m, 4H), 0.99–0.77 (m, 6H).

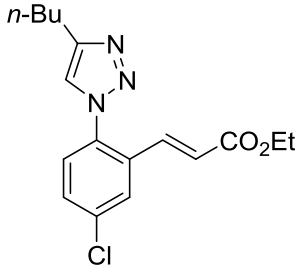
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 196.0 (C_q), 148.8 (C_q), 138.1 (C_q), 137.5 (C_q), 136.2 (C_q), 131.1 (CH), 129.0 (CH), 125.6 (CH), 122.3 (CH), 31.5 (CH_2), 26.8 (CH_3), 25.2 (CH_2), 22.2 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ =3134, 3066, 2956, 2930, 2861, 1686, 1607, 1557, 1436, 1358, 1249, 1179, 1038, 962, 906, 830, 657, 595 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 507 (48) [M+Na^+], 485 (100) [M+H^+], 429 (6), 396 (2).

HR-MS (ESI) *m/z* calcd for $C_{28}H_{32}N_6O_2$, [M+H^+] 485.2659, found 485.2660.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-5-chlorophenyl]acrylate (134jc)



The general procedure **E** was followed using 4-*n*-butyl-1-(4-chlorophenyl)-1*H*-1,2,3-triazole (**123j**) (235.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.8 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1) yielded **134jc** (177 mg, 53%) as a colorless solid.

M.p.: 74 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 2.1 Hz, 1H), 7.50–7.43 (m, 2H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 15.9 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H),

2.79 (t, *J* = 7.4 Hz, 2H), 1.79–1.62 (m, 2H), 1.50–1.35 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H).

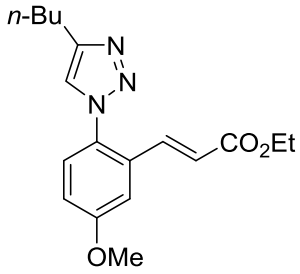
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.6 (C_q), 149.0 (C_q), 137.3 (CH), 135.9 (C_q), 134.9 (C_q), 131.8 (C_q), 130.6 (CH), 127.8 (CH), 123.4 (CH), 123.4 (CH), 123.0 (CH), 60.9 (CH_2), 31.5 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2931, 1712, 1493, 1241, 1178, 1038, 981, 751 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 372 (100) [M+K$^+$], 356 (37) [M+Na$^+$], 334 (65) [M+H$^+$], 260 (6), 189 (2), 173 (7).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{21}ClN_3O_2$, [M+H$^+$] 334.1317, found 334.1317.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-5-methoxyphenyl]acrylate (134kc)



The general procedure **E** was followed using 4-*n*-butyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (**123k**) (231.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134kc** (182 mg, 55%) as a colorless solid.

M.r.: 70–73 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 16.0 Hz, 1H), 7.19 (d, *J* = 2.8 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 2.81 (t, *J* = 7.7 Hz, 2H), 1.81–1.66 (m, 2H), 1.49–1.33 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

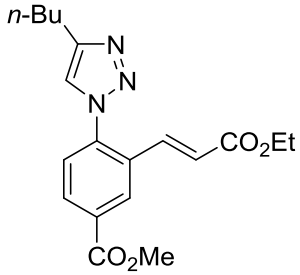
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.1 (C_q), 160.5 (C_q), 148.7 (C_q), 138.5 (CH), 131.8 (C_q), 129.9 (C_q), 128.1 (CH), 123.4 (CH), 122.3 (CH), 116.5 (CH), 112.1 (CH), 60.9 (CH_2), 55.9 (CH_3), 31.7 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 14.4 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2934, 1710, 1634, 1504, 1185, 1034, 855, 499 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 368 (100) [M+K$^+$], 352 (14) [M+Na$^+$], 330 (41) [M+H$^+$], 290 (2), 255 (5), 217 (17), 190 (2), 169 (7), 152 (24), 108 (13).

HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}N_3O_3$, [M+H$^+$] 330.1812, found 330.1798.

Synthesis of Methyl (*E*)-4-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-3-(3-ethoxy-3oxyprop-1-*n*-1-yl)benzoate (134lc)



The general procedure **E** was followed using methyl 4-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)benzoate (**123l**) (259.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134lc** (196 mg, 55%) as a colorless solid.

M.p.: 55 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.40 (d, J = 1.9 Hz, 1H), 8.15 (dd, J = 8.3, 1.9 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 7.48 (d, J = 16.0 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 2.81 (t, J = 7.4 Hz, 2H), 1.80–1.65 (m, 2H), 1.51–1.34 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H).

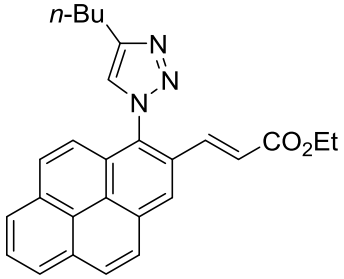
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.8 (C_q), 165.5 (C_q), 149.2 (C_q), 139.5 (C_q), 137.9 (CH), 131.5 (CH), 131.4 (C_q), 130.2 (C_q), 129.4 (CH), 126.5 (CH), 123.3 (CH), 122.9 (CH), 60.9 (CH_2), 52.8 (CH_3), 31.5 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2958, 1722, 1366, 1264, 1204, 984, 769, 751 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 396 (100) [M+K$^+$], 380 (15) [M+Na$^+$], 358 (24) [M+H$^+$], 217 (10), 169 (3), 152 (9).

HR-MS (ESI) *m/z* calcd for $C_{19}H_{24}N_3O_4$, [M+H$^+$] 358.1761, found 358.1752.

Synthesis of Ethyl (*E*)-3-[1-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)pyrenyl]acrylate (134pc)



The general procedure **E** was followed using 4-*n*-butyl-1-(pyren-1-yl)-1*H*-1,2,3-triazole (**123p**) (162.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.1 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (199.6 mg, 2.00 mmol) and $AgSbF_6$ (50.1 mg, 30 mol %). Purification by column chromatography (n-pentane/EtOAc 6/1) yielded **134pc** (59 mg, 28%) as a yellow solid.

M.p.: 123 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.46 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.11–8.05 (m, 3H), 7.66 (s, 1H), 7.44 (d, J = 16.0 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.98 (t, J = 7.7 Hz, 2H), 1.93–1.78 (m, 2H), 1.57–1.48 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H).

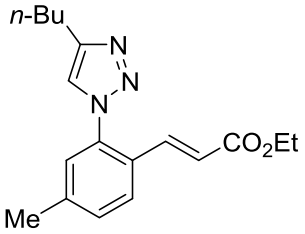
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.2 (C_q), 148.9 (C_q), 138.9 (CH), 132.4 (C_q), 131.3 (C_q), 130.9 (C_q), 130.3 (CH), 129.8 (CH), 129.6 (C_q), 129.6 (C_q), 128.7 (C_q), 127.4 (CH), 127.1 (CH), 126.8 (CH), 126.6 (CH), 125.5 (C_q), 125.3 (CH), 123.9 (C_q), 122.9 (CH), 122.6 (CH), 121.5 (CH), 60.9 (CH_2), 31.8 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 14.4 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2929, 1714, 1636, 1259, 1177, 1036, 821, 705 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 423 (100) [M+K$^+$], 424 (65) [M+H$^+$], 397 (3), 369 (2), 326 (2), 247 (6), 217 (4), 160 (3), 117 (10).

HR-MS (ESI) *m/z* calcd for $C_{27}H_{26}N_3O_2$, [M+H$^+$] 424.2020, found 424.2009.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-4-methylphenyl]acrylate (134cc)

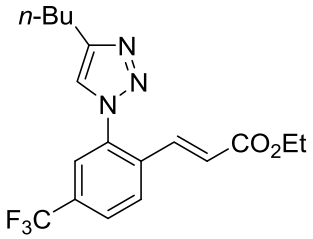


The general procedure **E** was followed using 4-*n*-butyl-1-(*m*-tolyl)-1*H*-1,2,3-triazole (**123c**) (215.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.8 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1 → 2/1) yielded **134cc** (202 mg, 65%) as a colorless solid.

M.r.: 71–72 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.39 (d, J = 16 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.30 (s, 1H), 6.32 (d, J = 16 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 1.74 (p, J = 7.5 Hz, 2H), 1.49–1.39 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166,3 (C_q),148.8 (C_q), 141.7 (C_q), 138.5 (CH), 136.5 (C_q), 130.8 (CH), 127.6 (CH), 127.5 (C_q), 127.3 (CH), 123.2 (CH), 121.2 (CH), 60.8 (CH_2), 31.7 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 21.3 (CH_3), 14.4 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2929, 1705, 1634, 1510, 1365, 1179, 1035, 822, 474 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 352 (94) [M+K$^+$], 336 (27) [M+Na$^+$], 314 (100) [M+H$^+$], 240 (15).
HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}N_3O_2$, [M+H$^+$] 314.1863, found 314.1867.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-4-(trifluoromethyl)phenyl]acrylate (134mc)



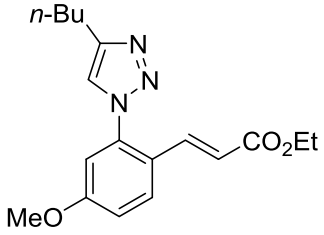
The general procedure **E** was followed using 4-*n*-butyl-1-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (**123m**) (269.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 19/1 → 2/1) yielded **134mc** (227 mg, 62%) as a colorless solid.

M.r.: 93–95 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.8 Hz, 1H), 7.79–7.75 (m, 2H), 7.54 (s, 1H), 7.44 (d, J = 16.0, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.83 (t, J = 7.7 Hz, 2H), 1.84–1.67 (m, 2H), 1.51–1.36 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.6 (C_q), 149.4 (C_q), 137.3 (CH), 136.7 (C_q), 133.8 (C_q), 132.8 ($^2J_{C\text{-}F}$ = 34 Hz, C_q), 128.7 (CH), 126.6 ($^3J_{C\text{-}F}$ = 4 Hz, CH), 124.5 (CH), 123.8 ($^3J_{C\text{-}F}$ = 2 Hz, CH), 123.1 ($^1J_{C\text{-}F}$ = 273 Hz, C_q), 123.0 (CH), 61.2 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).
^{19}F-NMR (283 MHz, $CDCl_3$): δ = -62.9 (s).
IR (ATR): $\tilde{\nu}$ = 2959, 1705, 1469, 1323, 1273, 1123, 1941, 841 cm^{-1}.

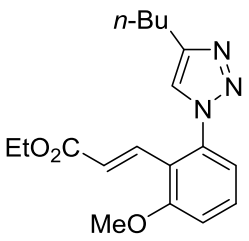
MS (ESI) *m/z* (relative intensity): 406 (100) [M+K$^+$], 390 (23) [M+Na$^+$], 368 (36) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{18}H_{21}F_3N_3O_2$, [M+H$^+$] 368.1580, found 368.1577.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-4-methoxyphenyl]acrylate (134dc) and Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-6-methoxyphenyl]acrylate (134dc')

The general procedure **E** was followed using 4-*n*-butyl-1-(3-methoxyphenyl)-1*H*-1,2,3-triazole (**123d**) (231.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 9/1) yielded **134dc** (122 mg, 37%) and **134dc'** (95 mg, 29%) as colorless solids.



M.p.: 66 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.7 Hz, 1H), 7.49 (s, 1H), 7.36 (d, *J* = 15.9 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 2.82 (t, *J* = 7.6 Hz, 2H), 1.82–1.66 (m, 2H), 1.52–1.36 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.5 (C_q), 161.5 (C_q), 148.9 (C_q), 138.2 (CH), 137.8 (C_q), 128.9 (CH), 123.3 (CH), 122.5 (C_q), 119.8 (CH), 116.6 (CH), 111.6 (CH), 60.7 (CH_2), 55.9 (CH_3), 31.7 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 14.4 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2962, 1706, 1635, 1279, 1259, 1164, 1023, 816 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 368 (100) [M+K$^+$], 352 (37) [M+Na$^+$], 330 (64) [M+H$^+$], 256 (12), 173 (6).
HR-MS (ESI) *m/z* calcd for $C_{18}H_{23}N_3O_3$, [M+H$^+$] 330.1812, found 330.1813.



M.r.: 94–95 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44–7.37 (m, 2H), 7.28 (d, J = 16.2 Hz, 1H), 7.08–7.01 (m, 2H), 6.32 (d, J = 16.2 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 2.78 (t, J = 7.5 Hz, 2H), 1.77–1.61 (m, 2H), 1.47–1.32 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 167.0 (C_q), 159.4 (C_q), 148.7 (C_q), 137.9 (C_q), 134.6 (CH), 130.6 (CH), 124.5 (CH), 123.3 (CH), 119.8 (C_q), 119.3 (CH), 112.4 (CH), 60.6 (CH_2), 56.2 (CH_3), 31.7 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

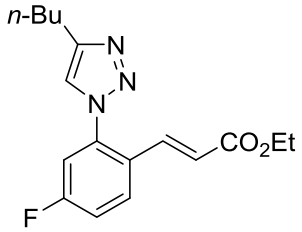
IR (ATR): $\tilde{\nu}$ = 2959, 1704, 1481, 1274, 1188, 1174, 797, 756 cm^{-1}.

MS (EI) *m/z* (relative intensity): 329 (2) [M^+], 256 (58), 228 (100), 213 (22), 198 (20), 186 (41), 173 (34), 43 (21).

HR-MS (EI) *m/z* calcd for $C_{18}H_{24}N_3O_3$, [M^+] 329.1739, found 329.1741.

Synthesis of Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-4-fluorophenyl]acrylate (134ec) and Ethyl (*E*)-3-[2-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-6-fluorophenyl]acrylate (134ec')

The general procedure **E** was followed using 4-*n*-butyl-1-(3-fluorophenyl)-1*H*-1,2,3-triazole (**123e**) (219.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.8 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134ec** (48 mg, 15%) and **134ec'** (133 mg, 42%) as colorless solids.



M.p.: 66 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.81–7.69 (m, 1H), 7.50 (s, 1H), 7.39 (d, J = 15.9 Hz, 1H), 7.30–7.20 (m, 2H), 6.33 (d, J = 15.9 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 1.85–1.64 (m, 2H), 1.51–1.36 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H).

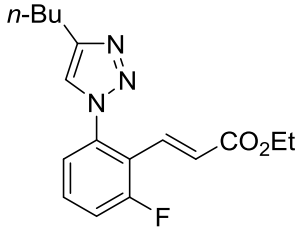
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.9 (C_q), 163.4 ($^1J_{C\text{-}F}$ = 254 Hz, C_q), 149.2 (C_q), 137.7 (CH), 137.6 (C_q), 129.7 ($^3J_{C\text{-}F}$ = 9 Hz, CH), 126.5 ($^3J_{C\text{-}F}$ = 4 Hz, C_q), 123.0 (CH), 122.1 ($^5J_{C\text{-}F}$ = 2 Hz, CH), 117.4 ($^2J_{C\text{-}F}$ = 22 Hz, CH), 114.1 ($^2J_{C\text{-}F}$ = 25 Hz, CH), 60.9 (CH_2), 31.6 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.4 (CH_3), 13.9 (CH_3).

^{19}F-NMR (283 MHz, $CDCl_3$): δ = -107.8 (td, J = 8.1, 5.7 Hz).

IR (ATR): $\tilde{\nu}$ = 2932, 1716, 1183, 1163, 1043, 975, 509 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 356 (100) [M+K^+], 340 (43) [M+Na^+], 318 (66) [M+H^+], 244 (9), 173 (5).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{21}FN_3O_2$, [M+H^+] 318.1612, found 318.1616.



M.r.: 73–74 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.52–7.38 (m, 2H), 7.35–7.24 (m, 2H), 7.20 (d, *J* = 16.3 Hz, 1H), 6.42 (d, *J* = 16.4, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 1.79–1.59 (m, 2H), 1.52–1.36 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.2 (C_q), 161.5 ($^1J_{C\text{-}F}$ = 256 Hz, C_q), 149.0 (C_q), 137.7 ($^3J_{C\text{-}F}$ = 5 Hz, C_q), 132.3 (CH), 130.9 ($^5J_{C\text{-}F}$ = 10 Hz, CH), 126.3 ($^3J_{C\text{-}F}$ = 13 Hz, CH), 123.1 (CH), 122.8 ($^4J_{C\,F}$ = 3 Hz, CH), 119.5 ($^2J_{C\text{-}F}$ = 14 Hz, C_q), 117.6 ($^2J_{C\text{-}F}$ = 23 Hz, CH), 60.9 (CH_2), 31.6 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

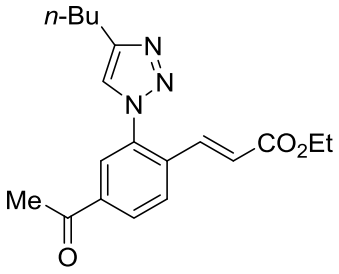
^{19}F-NMR (283 MHz, $CDCl_3$): δ = -109.0 (dd, *J* = 10.6, 5.6 Hz).

IR (ATR): $\tilde{\nu}$ = 2961, 1712, 1315, 1182, 982, 800, 751, 386 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 356 (100) [M+K^+], 318 (40) [M+H^+], 290 (2), 232 (7), 217 (16), 190 (2), 169 (5), 152 (17), 102 (10).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{21}FN_3O_2$, [M+H^+] 318.1612, found 318.1602.

Synthesis of Ethyl (*E*)-3-[4-acetyl-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)phenyl]acrylate (134nc) and 1,1'-[2',6-Bis(4-butyl-1*H*-1,2,3-triazol-1-yl)-(1,1'-biphenyl)-3,4'-diyl)bis(ethan-1-one) (143)



The general procedure **A** was followed using 1-[3-(4-*n*-butyl-1*H*-1,2,3-triazole-1-yl)phenyl]ethan-1-one (**123e**) (242.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50

mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.6 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 3/1) yielded **134ec** (58 mg, 17%) and **143** (53 mg, 11%) as colorless solids.

M.p.: 35°C

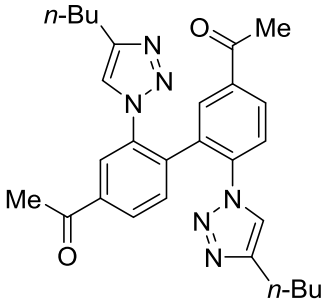
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.07 (ddd, *J* = 8.2, 1.8, 0.6 Hz, 1H), 8.01 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.54 (s, 1H), 7.43 (dd, *J* = 16.0, 0.6 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.82 (ddd, *J* = 8.7, 7.0, 0.7 Hz, 2H), 2.63 (s, 3H), 1.80–1.65 (m, 2H), 1.43 (dq, *J* = 14.7, 7.4 Hz, 2H) 1.27 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 196. 0 (C_q), 165.7 (C_q), 149.2 (C_q), 138.7 (C_q), 137.5 (CH), 136.7 (C_q), 134.5 (C_q), 129.3 (CH), 128.3 (CH), 126.4 (CH), 124.3 (CH), 123.0 (CH), 61.1 (CH_2), 31.6 (CH_2), 26.8 (CH_3), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3139, 2957, 2928, 2857, 1682, 1604, 1556, 1490, 1398, 1287, 1264, 1242, 1219, 819, 796, 681, 661, 586, 480 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 364 (53) [M+Na$^+$], 342 (100) [M+H$^+$], 314 (1), 268 (6), 242 (2).

HR-MS (ESI) *m/z* calcd for $C_{19}H_{24}N_3O_3$, [M+H$^+$] 342.1812, found 342.1818.



M.r.: 58−60°C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 1.7 Hz, 2H), 7.93 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.46 (d, *J* = 0.8 Hz, 2H), 7.26 (d, *J* = 0.9 Hz, 2H), 2.79–2.52 (m, 10H), 1.57 (dt, *J* = 15.2, 7.9 Hz, 4H), 1.39–1.12 (m, 4H), 0.99–0.77 (m, 6H).

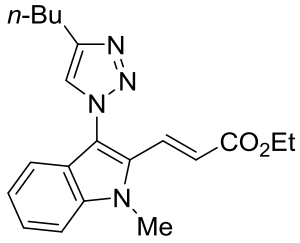
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 196.0 (C_q), 148.8 (C_q), 138.1 (C_q), 137.5 (C_q), 136.2 (C_q), 131.1 (CH), 129.0 (CH), 125.6 (CH), 122.3 (CH), 31.5 (CH_2), 26.8 (CH_3), 25.2 (CH_2), 22.2 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ =3134, 3066, 2956, 2930, 2861, 1686, 1607, 1557, 1436, 1358, 1249, 1179, 1038, 962, 906, 830, 657, 595 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 507 (48) [M+Na$^+$], 485 (100) [M+H$^+$], 429 (6), 396 (2).

HR-MS (ESI) *m/z* calcd for $C_{28}H_{32}N_6O_2$, [M+H$^+$] 485.2659, found 485.2660.

Synthesis of Ethyl (*E*)-3-[3-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-1-methyl-1H-indol-2-yl]acrylate (134oc)



The general procedure **E** was followed using methyl 3-(4-*n*-butyl-1*H*-1,2,3-triazol-1-yl)-1-methyl-1*H*-indole (**123o**) (127.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (199.6 mg, 1.00 mmol) and $AgSbF_6$ (51.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134oc** (176 mg, 50%) as a yellow solid.

M.p.: 70 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 16.3 Hz, 1H), 7.53 (s, 1H), 7.44–7.33 (m, 3H), 7.18 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H), 5.92 (d, J = 16.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 2.86 (t, J = 8.1 Hz, 2H), 1.83–1.68 (m, 2H), 1.53–1.36 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H).

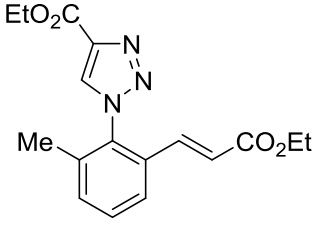
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.5 (C_q), 148.7 (C_q), 136.8 (C_q), 129.4 (CH), 129.1 (C_q), 125.2 (CH), 123.6 (C_q), 123.4 (CH), 122.0 (CH), 121.9 (CH), 118.4 (CH), 115.9 (C_q), 110.1 (CH), 60.9 (CH_2), 31.6 (CH_2), 31.2 (CH_3), 25.5 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2933, 1708, 1624, 1278, 1185, 1034, 844, 738 cm^{-1}.

MS (EI) *m/z* (relative intensity): 352 (4) [M$^+$], 324 (8), 251 (100), 221 (15), 208 (24), 195 (45), 181 (16), 43 (24).

HR-MS (EI) *m/z* calcd for $C_{20}H_{24}N_4O_2$, [M$^+$] 352.1899, found 352.1897.

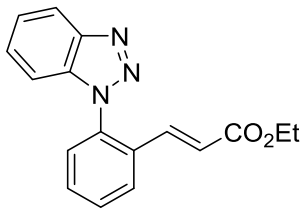
Synthesis of Ethyl (*E*)-1-[2-(3-ethoxy-3-oxoprop-1-en-1-yl)-6-methylphenyl]-1*H*-1,2,3-triazole-4-carboxylate (134qc)



The general procedure **E** was followed using ethyl 1-(*o*-tolyl)-1*H*- 1,2,3-triazole-4-carboxylate (**123q**) (115.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (75.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (119.0 mg, 1.20 mmol) and $AgSbF_6$ (50.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 3/1) yielded **134qc** (62 mg, 38%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 7.63–7.58 (m, 1H), 7.49 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.40 (ddd, *J* = 7.7, 1.6, 0.8 Hz, 1H), 6.98 (d, *J* = 15.9 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.04 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.9 (C_q), 160.7 (C_q), 140.7 (C_q), 137.5 (CH), 136.5 (C_q), 134.7 (C_q), 132.6 (CH), 132.6 (C_q), 131.1 (CH), 130.1 (CH), 125.2 (CH), 123.1 (CH), 61.8 (CH_2), 60.9 (CH_2), 17.5 (CH_3), 14.5 (CH_3), 14.3 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3133, 2982, 1719, 1541, 1503, 1335, 1227, 1202, 1145, 116, 1034, 987, 834, 764, 715, 456 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 352 (10) $[M+Na^+]$, 330 (100) $[M+H^+]$.
HR-MS (ESI) *m/z* calcd for $C_{17}H_{20}N_3O_4$, $[M+H^+]$ 330.1448, found 330.1455.

Synthesis of Ethyl (*E*)-3-[2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)phenyl]acrylate (134sc):



The general procedure **E** was followed using 1-phenyl-1*H*-benzo[*d*][1,2,3]triazole (**123s**) (91.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (75.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (119.0 mg, 1.20 mmol) and $AgSbF_6$ (50.0 mg, 30 mol %). Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded **134sc** (30 mg, 20%) as a colorless solid.

M.r.: 81-82 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.93–7.80 (m, 1H), 7.65–7.55 (m, 2H), 7.55–7.37 (m, 3H), 7.36–7.25 (m, 1H), 7.24 (s, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.1 (C_q), 146.0 (C_q), 138.5 (CH), 135.5 (C_q), 134.4 (C_q), 131.6 (C_q), 131.1 (CH), 130.3 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 124.6 (CH), 122.1 (CH), 120.5 (CH), 110.2 (CH), 60.8 (CH_2), 14.3 (CH_3).

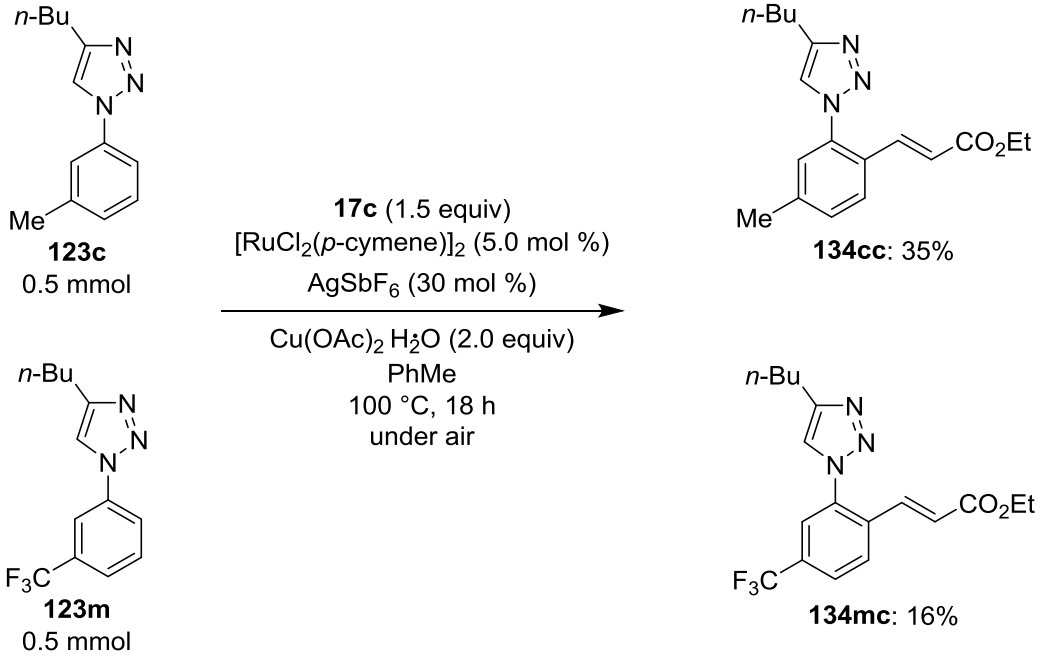
IR (ATR): $\tilde{\nu}$ = 3074, 2982, 1708, 1639, 1490, 1367, 1321, 1299, 1272 1179 976, 915, 873, 836, 750, 666, 590, 574, 484, 460, 435, 420 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 332 (33) [M+K^+], 316 (100) [M+Na^+], 294 (92) [M+H^+], 220 (19), 166 (6).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{16}N_3O_2$, [M+H^+] 294.1237, found 294.1239.

5.3.6 Intermolecular Competition Experiment for the Ruthenium-Catalyzed Synthesis of Alkenylated *N*-Aryl-1,2,3-triazoles

Competition Experiment between *N*-Aryl-1,2,3-triazoles 123c and 123m

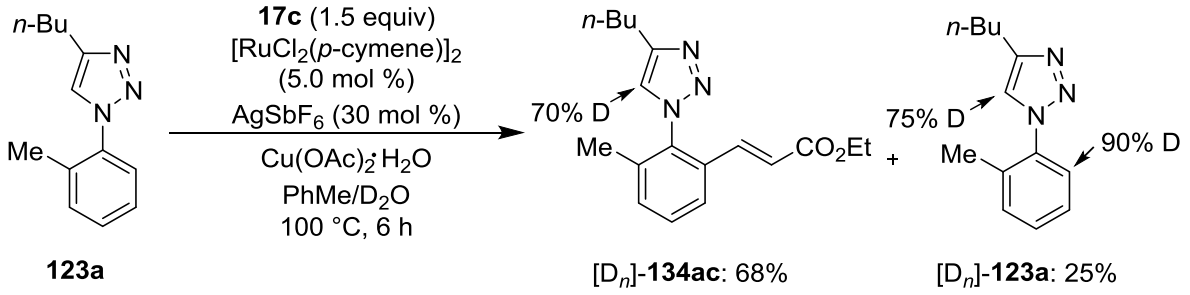


A mixture of 4-*n*-butyl-1-(*m*-tolyl)-1*H*-1,2,3-triazole (**123c**) (107.0 mg, 0.50 mmol), 4-*n*-butyl-1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazole (**123m**) (134.5 mg, 0.50 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (399.3 mg, 2.00 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %) in PhMe (4.0 mL) was stirred at 100 °C for 18 h under air. At ambient temperature, the reaction mixture was diluted with sat. aq. NH_4Cl/NH_3 (1:1, 10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent in *vacuo*, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc 19/1) to yield **134cc** (111 mg, 35%) and **134mc** (59 mg, 16%).

5.3.7 Mechanistic Studies on the Ruthenium(II)-Catalyzed Synthesis of Alkenylated *N*-Aryl-1,2,3-triazoles

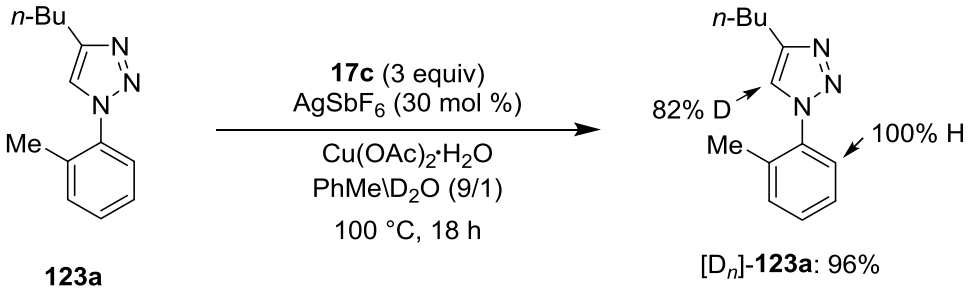
Ruthenium-Catalyced H/D Exchange in Substrates 140a and 145ac with D_2O as the Cosolvent

The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (107.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (239.8 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %) in a solvent mixture of PhMe and D_2O (1.8/0.2 mL) at 100 °C for 6 h. Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded $[D]_n$-**134ac** (212 mg, 68%) as a colorless oil and reisolated starting material $[D]_n$-**123a** (54 mg, 25%). The D-incorporation in $[D]_n$-**123a** was estimated by ^{1}H-NMR spectroscopy.



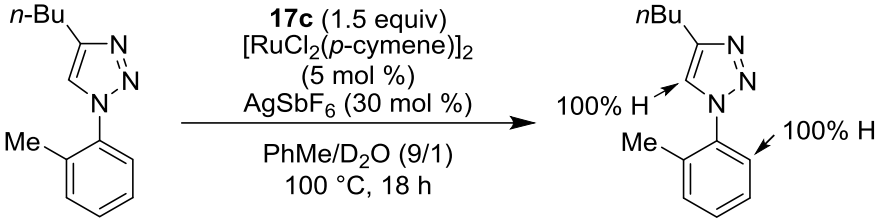
Ruthenium-Catalyzed H/D Exchange in Substrates 123a with D_2O as the Cosolvent

The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (107.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (239.8 mg, 1.20 mmol) and $AgSbF_6$ (103.0 mg, 30 mol %) in a solvent mixture of PhMe and D_2O (1.8/0.2 mL) at 100 °C for 18 h. Purification by column chromatography (*n*-pentane/EtOAc 6/1) yielded reisolated starting material $[D]_n$-**123a** (103 mg, 96%). The D-incorporation in $[D]_n$-**123a** was estimated by ^{1}H-NMR spectroscopy.



Ruthenium(II)-Catalyced H/D Exchange in Substrate 140a with D_2O as the Cosolvent

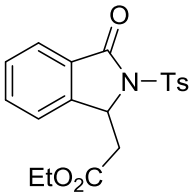
The general procedure **E** was followed using 4-*n*-butyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole (**123a**) (107.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (150.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5 mol %) and $AgSbF_6$ (103.0 mg, 30 mol %) in a solvent mixture of PhMe and D_2O (1.8/0.2 mL) was stirred at 100 °C for 18 h. Purification by column chromatography (*n*-pentane/EtOAc 6/1) reisolated starting material $[D]_n$-**123a** (54 mg, 25%). The D-incorporation in $[D]_n$-**123a** was estimated by ^{1}H-NMR spectroscopy.



123a [D_n]-**123a**: 94%

5.3.8 Ruthenium(II)-Catalyzed Synthesis of Isoindolinones

Synthesis of Ethyl 2-(3-oxo-2-tosylisoindolin-1-yl)acetate 136ac



The general procedure **F** was followed using *N*-tosylbenzamide (**135a**) (275.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ac** (194 mg, 52%) as a colorless solid.

M.r.: 138–139 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.62 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.55−7.43 (m, 2H), 7.36−7.30 (m, 2H), 5.60 (dd, *J* = 8.1, 3.4 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.55 (dd, *J* = 16.6, 3.4 Hz, 1H), 2.95 (dd, *J* = 16.6, 8.1 Hz, 1H), 2.42 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.7 (C_q), 166.4 (C_q), 145.3 (C_q), 145.3 (C_q), 135.8 (C_q), 134.3 (CH), 129.7 (CH), 129.4 (CH), 129.3 (C_q), 128.4 (CH), 125.0 (CH), 123.1 (CH), 62.2 (CH_2), 58.5 (CH), 39.5 (CH_2), 21.9 (CH_3), 14.2 (CH_3).

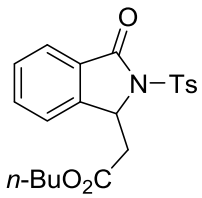
IR (ATR): $\tilde{\nu}$ = 2987, 2941, 2876, 1720, 1359, 1166, 1086, 824, 737, 685 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 396 (95) $[M+Na^+]$, 374 (100) $[M+H^+]$.

HR-MS (ESI) *m/z* calcd for $C_{19}H_{20}NO_5S$, $[M+H^+]$ 374.1057, found 374.1054.

The spectral data are in accordance with those reported in the literature.[109b]

Synthesis of *n*-Butyl 2-(3-oxo-2-tosylisoindolin-1-yl)acetate 136ae



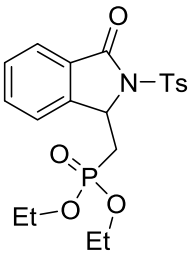
The general procedure **F** was followed using *N*-tosylbenzamide (**135a**) (275.3 mg, 1.00 mmol), *n*-butyl acrylate (**17c**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg,

5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ae** (189 mg, 47%) as a colorless solid.

M.r.: 80–83 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.62 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 7.51−7.41 (m, 2H), 7.37−7.28 (m, 2H), 5.60 (dd, *J* = 8.1, 3.4 Hz, 1H), 4.01 (dd, *J* = 6.8, 0.7 Hz, 2H), 3.55 (dd, *J* = 16.6, 3.4 Hz, 1H), 2.95 (dd, *J* = 16.6, 8.1 Hz, 1H), 2.42 (s, 3H), 2.17 (s, 3H) 1.55−1.42 (m, 2H), 1.35−1.17 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 166.4 (C_q), 145.4 (C_q), 145.3 (C_q), 135.8 (C_q), 134.3 (CH), 129.7 (CH), 129.4 (C_q), 129.2 (CH), 128.4 (CH), 125.0 (CH), 123.1 (CH), 65.1 (CH_2), 58.6 (CH), 39.5 (CH_2), 30.6 (CH_2), 21.9 (CH_3), 19.2 (CH_2), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2957, 1718, 1348, 1295, 1166, 1092, 816, 665, 653, 601 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 440 (69) [M+K^+], 424 (62) [M+Na^+], 402 (100) [M+H^+].
HR-MS (ESI) *m/z* calcd for $C_{21}H_{24}NO_5S$, [M+H^+] 401.1297, found 402.1370.

Synthesis of Diethyl [(3-oxo-2-tosylisoindolin-1-yl)methyl]phosphonate 136ak



The general procedure **F** was followed using *N*-tosylbenzamide (**135a**) (275.3 mg, 1.00 mmol), diethyl vinylphosphonate (**17k**) (158.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (EtOAc) yielded **136ak** (201 mg, 46%) as a colorless solid.

M.r.: 127–128 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 5.47 (ddd, *J* = 18.9, 8.7, 2.5 Hz, 1H), 4.11 (m, 2H), 3.97 (dq, *J* = 8.2, 7.1 Hz, 2H), 3.04 (ddd, *J* = 21.8, 15.5, 2.5 Hz, 1H), 2.53 (td, *J* = 7,6 1.2 Hz, 1H), 2.39 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 166.4 (C_q), 145.3 (C_q) 145.1 (d, $^3J_{C\text{-}P}$ = 1.4 Hz, C_q), 135.7 (C_q), 134.1 (CH), 129.7 (CH), 129.3 (CH), 129.1 (C_q), 128.4 (CH), 124.8 (CH), 124.4 (CH),

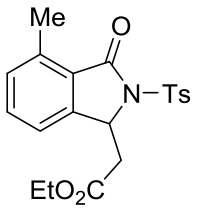
62.2 (dd, $^{3}J_{C\text{-}P}$ = 50.2, 6.6 Hz, CH_2), 56.9 ($^{3}J_{C\text{-}P}$ = 1.6 Hz, CH), 31.4 ($^{1}J_{C\text{-}P}$ = 139.5 Hz, CH_2), 16.4 (CH_3), 16.3 ($^{3}J_{C\text{-}P}$ = 6.2 Hz, CH_3).

IR (ATR): $\tilde{\nu}$ = 2979, 2926, 1722, 1360, 1173, 1095, 1035, 957, 772, 665 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 460 (76) [M+Na^+], 438 (100) [M+H^+].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{25}NO_6PS$, [M+H^+] 438.1135, found 438.1133.

Synthesis of Ethyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136bc



The general procedure **F** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (289.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136bc** (286 mg, 74%) as a colorless solid.

M.r.: 99–101 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.36-7.28 (m, 3H), 7.28−7.23 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 5.53 (dd, *J* = 7.1, 3.5 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.45 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.93 (dd, *J* = 16.5, 7.7 Hz, 1H), 2.58 (s, 3H), 2.40 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).

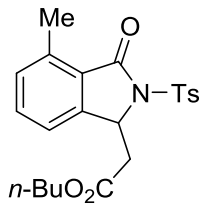
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.9 (C_q), 167.2 (C_q), 146.0 (C_q), 145.2 (C_q), 139.7 (C_q), 136.1 (C_q), 133.8 (CH), 131.2 (CH), 129.8 (CH), 128.5 (CH), 126.6 (C_q), 120.4 (CH), 61.1 (CH_2), 57.6 (CH), 39.6 (CH_2), 21.8 (CH_3), 17.8 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2932, 2921, 1715, 1379, 1190, 1170, 1102, 1043, 750, 706 cm^{-1}.

MS (EI) *m/z* (relative intensity): 323 (95), 300 (20), 250 (57), 232 (100), 186 (18), 155 (46), 91 (62), 65 (37).

HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}NO_5S$, [M+H^+] 388.1213, found 388.1213.

Synthesis of *n*-Butyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136be



The general procedure **F** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (289.3 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), $RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136be** (366 mg, 88%) as a colorless solid.

M.r.: 93–95 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 2H), 7.46 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 6.7 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 5.55 (dd, *J* = 7.7, 3.4 Hz, 1H), 4.00 (td, *J* = 6.7, 2.5 Hz, 2H), 3.48 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.96 (dd, *J* = 16.5, 7.7 Hz, 1H), 2.60 (s, 3H), 2.42 (s, 3H), 1.55−1.40 (m, 2H), 1.37−1.10 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H).

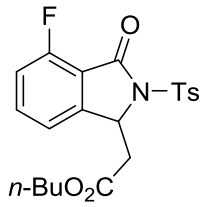
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 167.0 (C_q), 146.0 (C_q), 145.1 (C_q), 139.7 (C_q), 136.0 (C_q), 133.7 (CH), 131.1 (CH), 129.7 (CH), 128.4 (CH), 126.5 (C_q), 120.3 (CH), 65.0 (CH_2), 57.6 (CH), 39.6 (CH_2), 30.6 (CH_2), 21.9 (CH_3), 19.2 (CH_2), 17.8 (CH_3), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2961, 1719, 1599, 1355, 1166, 1104, 815, 665, 576, 543 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 454 [M+K$^+$] (100), 438 (79) [M+Na$^+$], 416 (89) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{22}H_{26}NO_5S$, [M+H$^+$] 416.1526, found 416.1529.

Synthesis of *n*-Butyl 2-(4-fluoro-3-oxo-2-tosylisoindolin-1-yl)acetate 136ce



The general procedure **F** was followed using 2-fluoro-*N*-tosylbenzamide (**135c**) (275.3 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ce** (327 mg, 78%) as a colorless solid.

M.r.: 98–101 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 8.0, 4.8 Hz, 1H), 7.36−7.28 (m, 4H), 5.58 (dd, J = 7.9, 3.3 Hz, 1H), 4.12−3.89 (m, 2H), 3.50 (dd, J = 16.7, 3.3 Hz, 1H), 3.00 (dd, J = 16.7, 7.9 Hz 1H), 2.42 (s, 3H), 1.56−1.43 (m, 2H), 1.37−1.19 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 163.0 ($^3J_{C\text{-}F}$ = 2.5 Hz, C_q), 159.4 ($^1J_{C\text{-}F}$ = 264.4 Hz, C_q), 147.6 ($^3J_{C\text{-}F}$ = 1.9 Hz, C_q), 145.4 (C_q), 136.3 ($^3J_{C\text{-}F}$ = 7.9 Hz, CH), 135.5 (C_q), 129.7 (CH), 128.6 (CH), 119.0 ($^4J_{C\text{-}F}$ = 4.3 Hz, CH), 117.2 ($^2J_{C\text{-}F}$ = 13.1 Hz, C_q), 116.4 ($^2J_{C\text{-}F}$ = 18.6 Hz, CH), 65.2 (CH_2), 58.1 (CH), 39.3 (CH_2), 30.6 (CH_2), 21.9 (CH_3), 13.8 (CH_3).

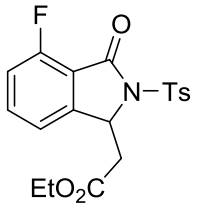
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -114.9 (dd, J = 9.0, 4.9 Hz).

IR (ATR): $\tilde{\nu}$ = 2960, 1978, 1724, 1379, 1165, 1084, 815, 692, 659, 577 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 458 (60) [M+K$^+$], 442 (47) [M+Na$^+$], 420 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{23}FNO_5S$, [M+H$^+$] 420.1275, found 420.1277.

Synthesis of Ethyl 2-(4-fluoro-3-oxo-2-tosylisoindolin-1-yl)acetate 136cc



The general procedure **F** was followed using 2-fluoro-*N*-tosylbenzamide (**135c**) (293.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136cc** (309 mg, 79%) as a colorless solid.

M.r.: 80–83 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 8.0, 4.8 Hz, 1H), 7.34-7.26 (m, 3H), 7.15−7.00 (m, 1H), 5.58 (dd, J = 7.9, 3.3 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.48 (dd, J = 16.7, 3.3 Hz, 1H), 2.99 (dd, J = 16.7, 7.8 Hz, 1H), 2.42 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H).

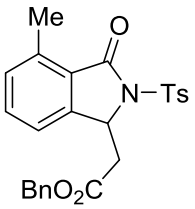
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.6 (C_q), 163.1 ($^3J_{C\text{-}F}$ = 2.7 Hz, C_q), 159.6 ($^1J_{C\text{-}F}$ = 264.7 Hz, C_q), 147.6 ($^3J_{C\text{-}F}$ = 1.9 Hz, C_q), 145.5 (C_q), 136.4 ($^3J_{C\text{-}F}$ = 8.0 Hz, CH), 135.6 (C_q), 129.8 (CH), 128.6 (CH), 119.1 ($^4J_{C\text{-}F}$ = 4.4 Hz, CH), 117.2 ($^2J_{C\text{-}F}$ = 13.0 Hz, C_q), 116.5 ($^2J_{C\text{-}F}$ = 18.7 Hz, CH), 61.2 (CH_2), 58.0 (CH), 39.3 (CH_2), 21.8 (CH_3), 14.1 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -114.9 (dd, J = 9.0, 4.8 Hz).

IR (ATR): $\tilde{\nu}$ = 2988, 2952, 1731, 1379, 1358, 1171, 1090,1020, 680, 658 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 430 (78) [M+K$^+$], 414 (67) [M+Na$^+$], 392 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{19}H_{19}FNO_5S$, [M+H$^+$] 392.0962, found 392.0963.

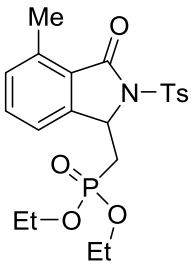
Synthesis of Benzyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136bd



The general procedure **F** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), benzyl acrylate (**17d**) (248.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (209.7 mg, 1.05 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136bd** (185 mg, 82%) as a colorless solid.

M.p.: 135 °C.
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.38-7.30 (m, 3H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.27−7.24 (m, 2H), 7.18−7.15 (m, 2H), 5.56 (dd, *J* = 7.9, 3.5 Hz, 1H), 5.06 (q, *J* = 12.2 Hz, 2H), 3.54 (dd, *J* = 16.4, 3.5 Hz, 1H), 2.99 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.57 (s, 3H), 2.42 (s, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 167.1 (C_q), 145.9 (C_q), 145.2 (C_q), 139.8 (C_q), 136.0 (C_q), 135.4 (C_q), 133.8 (CH), 131.2 (CH), 129.8 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 126.5 (C_q), 120.3 (CH), 67.0 (CH_2), 57.6 (CH), 39.7 (CH_2), 21.8 (CH_3), 17.7 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2953, 2189, 1731, 1424, 1238, 1203, 1129, 728, 693, 666, 543 cm^{-1}.
MS (EI) *m/z* (relative intensity): 449 (25) [M$^+$], 394 (43), 250 (28), 236 (13), 186 (12), 155 (23), 91 (100), 65 (17).
HR-MS (ESI) *m/z* calcd for $C_{25}H_{23}NO_5S$, [M$^+$] 449.1297, found 449.1288.

Synthesis of Diethyl [(4-methyl-3-oxo-2-tosylisoindolin-1-yl)methyl]phosphonate 136bk



The general procedure **F** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (289.3 mg, 1.00 mmol), diethyl vinylphosphonate (**17k**) (158.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (EtOAc) yielded **136bk** (216 mg, 48%) as a colorless solid.

M.p.: 121 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.33 (dd, J = 7.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.19 (dd, J = 7.5, 0.8 Hz, 1H), 5.44 (ddd, J = 19.2, 8.5, 2.4 Hz, 1H), 4.20−4.03 (m, 2H), 3.98 (dq, J = 8.0, 7.1 Hz, 2H), 3.01 (ddd, J = 21.8, 15.6, 2.5 Hz, 1H), 2.59 (s, 3H), 2.58−2.44 (m, 1H), 2.41 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H).

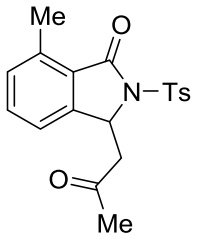
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 167.1 (C_q), 145.6 (d, $^3J_{C\text{-}P}$ = 1.6 Hz, C_q), 145.2 (C_q), 139.4 (C_q), 136.0 (C_q), 133.6 (CH), 131.1 (CH), 129.8 (CH), 128.5 (CH), 126.4 (C_q), 121.7 (CH), 62.0 (dd, $^2J_{C\text{-}P}$ = 48.9, 6.5 Hz, CH_2), 56.9 ($^2J_{C\text{-}P}$ = 1.6 Hz, CH), 31.5 ($^1J_{C\text{-}P}$ = 139.6 Hz, CH_2), 21.8 (CH_3), 17.7 (CH_3), 16.2 ($^3J_{C\text{-}P}$ = 18.0, 6.2 Hz, CH_3).

IR (ATR): $\tilde{\nu}$ = 2990, 2930, 1715, 1362, 1311, 1173, 1093, 1022, 943, 817 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 474 (100) [M+Na$^+$], 452 (67) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{21}H_{27}NO_6PS$, [M+H$^+$] 452.1289, found 452.1291.

Synthesis of 7-Methyl-3-(2-oxopropyl)-2-tosylisoindolin-1-one 136bj



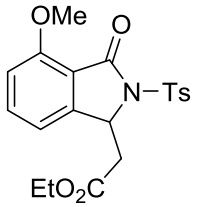
The general procedure **F** was followed using 3-methyl-*N*-tosylbenzamide (**135b**) (289.3 mg, 1.00 mmol), methyl vinylketone (**17j**) (67.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136bj** (89 mg, 25%) as a colorless solid.

M.r.: 169–172 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 8.4 Hz, 1H), 7.35−7.30 (m, 2H), 7.23-715 (m, 2H), 5.61 (dd, J = 8.5, 2.9, 0.7 Hz, 1H), 3.77 (dd, J = 18.0, 2.9 Hz, 2H), 3.77 (dd, J = 18.0, 2.9 Hz, 1H), 2.90 (dd, J = 18.0, 8.5 Hz, 1H), 2.57 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 205.3 (C_q), 167.0 (C_q), 146.9 (C_q), 145.1 (C_q), 139.6 (C_q), 135.7 (C_q), 133.9 (CH), 130.9 (CH), 129.7 (CH), 128.3 (CH), 126.0 (C_q), 120.6 (CH), 57.0 (CH), 49.2 (CH_2), 30.8 (CH_3), 21.9 (CH_3), 17.8 (CH_3).
IR (ATR): $\tilde{\nu}$ = 3097, 3033, 2927, 1727, 1704, 1351, 1164, 1104, 821, 782 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 396 (98) [M+K$^+$], 391 (100) [M+Na$^+$], 358 (44) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{19}H_{20}NO_4S$, [M+H$^+$] 358.1108, found 358.1105.

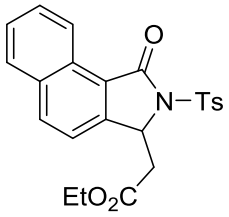
Synthesis of Ethyl 2-(4-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136dc



The general procedure **F** was followed using 2-methoxy-*N*-tosylbenzamide (**135d**) (305.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136dc** (210 mg, 52%) as a colorless solid.

M.r.: 120–122 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.37−7.28 (m, 2H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.53 (dd, *J* = 7.9, 3.4 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.47 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.91 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.40 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 164.7 (C_q), 158.5 (C_q), 147.9 (C_q), 145.0 (C_q), 136.1 (CH), 135.9 (C_q), 129.6 (CH), 128.6 (CH), 116.6 (C_q), 114.7 (CH), 111.0 (CH), 61.1 (CH_2), 57.5 (CH), 56.1 (CH_3), 39.8 (CH_2), 21.9 (CH_3), 13.9 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2987, 2944, 2247, 1742, 1710, 1597, 1487, 1378, 1184, 1168 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 426 (100) [M+K$^+$], 421 (71) [M+Na$^+$], 404 (50) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}NO_6S$, [M+H$^+$] 404.1162, found 404.1159.

Synthesis of Ethyl 2-(1-oxo-2-tosyl-2,3-dihydro-1*H*-benzo[*e*]isoindol-3-yl)acetate 136ec



The general procedure **F** was followed using *N*-tosyl-1-naphtamide (**135e**) (325.4 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ec** (288 mg, 68%) as a colorless solid.

M.p.: 149 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.02 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 3H), 7.90 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.69−7.48 (m, 3H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.68 (dd, *J* = 7.8, 3.5 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 16.5, 3.5 Hz, 1H), 3.02 (dd, *J* = 16.5, 7.8 Hz, 1H), 2.42 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H).

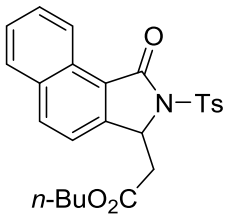
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.0 (C_q), 167.3 (C_q), 146.9 (C_q), 145.3 (C_q), 136.0 (C_q), 135.7 (CH), 133.4 (C_q), 129.8 (CH), 129.3 (C_q), 129.2 (CH), 128.5 (CH), 128.5 (CH), 127.5 (CH), 123.9 (CH), 123.3 (C_q), 119.6 (CH), 61.2 (CH_2), 58.0 (CH), 39.2 (CH_2), 21.8 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2966, 1721, 1360, 1324, 1165, 1113, 1092, 817, 793, 772 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 446 [M+K$^+$] (100), 441 (33) [M+Na$^+$], 424 (22) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{23}H_{22}NO_5S$, [M+H$^+$] 424.1210, found 424.1213.

Synthesis of *n*-Butyl 2-(1-oxo-2-tosyl-2,3-dihydro-1*H*-benzo[*e*]isoindol-3-yl)acetate 136ee



The general procedure **F** was followed using *N*-tosyl-1-naphtamide (**135e**) (325.4 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg,

2.5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ee** (262 mg, 58%) as a colorless solid.

M.r.: 127–130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.01 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 3H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.69−7.57 (m, 2H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.67 (dd, *J* = 7.8, 3.5 Hz, 1H), 4.02 (q, *J* = 7.5 Hz, 2H), 3.59 (dd, *J* = 16.5, 3.5 Hz, 1H), 3.04 (dd, *J* = 16.5, 7.8 Hz 1H), 2.41 (s, 3H), 1.53−1.32 (m, 2H), 1,32−1.05 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H).

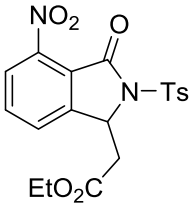
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.1 (C_q), 167.3 (C_q), 146.9 (C_q), 145.3 (C_q), 136.0 (C_q), 135.7 (CH), 133.4 (C_q), 129.8 (CH), 129.7 (CH), 129.3 (C_q), 129.2 (CH), 128.5 (CH), 127.5 (CH), 123.9 (CH), 123.3 (C_q), 119.6 (CH), 65.2 (CH_2), 58.0 (CH), 39.1 (CH_2), 30.6 (CH_2), 21.8 (CH_3), 19.1 (CH_2), 13.7 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2961, 1729, 1706, 1354, 1339, 1170, 1092, 965, 769, 663 cm^{-1}.

MS (EI) *m/z* (relative intensity): 451 (1) [M^+], 387 (35), 336 (14), 296 (100), 286 (46), 240 (12), 196 (55), 155 (32), 126 (22), 91 (86), 65 (16), 57 (31).

HR-MS (ESI) *m/z* calcd for $C_{25}H_{26}NO_5S$, [M+H^+] 452.1526, found 452.1526.

Synthesis of Ethyl 2-(4-nitro-3-oxo-2-tosylisonidolin-1-yl)acetate 136fc



The general procedure **F** was followed using 2-nitro-*N*-tosylbenzamide (**135f**) (320.0 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136fc** (247 mg, 59%) as a colorless solid.

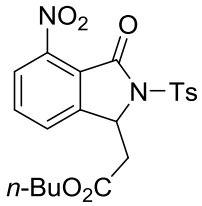
M.r.: 151–152 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.40−7.29 (m, 3H), 7.22−7.09 (m, 2H), 5.52 (dd, *J* = 8.3, 3.3 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.52 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.88 (dd, *J* = 16.5, 8.2 Hz, 1H), 2.41 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 166.4 (C_q), 160.6 (C_q), 145.2 (C_q), 137.7 (C_q), 135.8 (C_q), 130.6 (C_q), 129.7 (CH), 128.4 (CH), 124.1 (CH), 122.9 (CH), 107.0 (CH), 61.1 (CH_2), 58.3 (CH), 39.6 (CH_2), 21.9 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3093, 2988, 1729, 1533, 1359, 1317, 1168, 1104, 830, 725 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 457 (91) [M+K^+], 441 (100) [M+Na^+], 419 (33) [M+H^+].
HR-MS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_7S$, [M+H^+] 419.0907, found 419.0909.

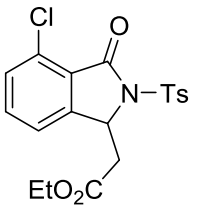
Synthesis of *n*-Butyl 2-(4-nitro-3-oxo-2-tosylisonidolin-1-yl)acetate 136fe



The general procedure **F** was followed using 2-nitro-*N*-tosylbenzamide (**135f**) (320.0 mg, 1.00 mmol), *n*-butyl acrylate (**17**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136f** (210 mg, 47%) as a colorless solid.

M.r.: 107–110 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 3H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.62 (dd, *J* = 7.8, 3.1 Hz, 1H), 3.98 (t, *J* = 6.8 Hz, 2H), 3.53 (dd, *J* = 17.0, 3.2 Hz, 1H), 3.07 (dd, *J* = 17.0, 7.8 Hz, 1H), 2.43 (s, 3H), 1.58−1.41 (m, 2H), 1.33−1.16 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.5 (C_q), 161.2 (C_q), 147.7 (C_q), 147.0 (C_q), 145.9 (C_q), 135.0 (C_q), 134.9 (CH), 129.9 (CH), 128.8 (CH), 127.2 (CH), 124.0 (CH), 121.7 (C_q), 65.4 (CH_2), 57.4 (CH), 38.7 (CH_2), 30.5 (CH_2), 21.9 (CH_3), 19.1 (CH_2), 13.7 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2976, 2936, 2873, 1716, 1596, 1399, 1347, 1193, 1104, 1063 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 485 (47) [M+K^+], 469 (56) [M+Na^+], 447 (100) [M+H^+].
HR-MS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_7S$, [M+H^+] 447.1220, found 447.1223.

Synthesis of Ethyl 2-(4-chloro-3-oxo-2-tosylisoindolin-1-yl)acetate 136gc



The general procedure **F** was followed using 2-chloro-*N*-tosylbenzamide (**135g**) (309.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (300.0 mg, 3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg,

5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136gc** (245 mg, 60%) as a colorless solid.

M.r.: 124–125 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 2H), 7.52 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.42−7.38 (m, 2H), 7.35−7.31 (m, 2H), 5.62−5.47 (m, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.47−3.41 (m, 1H), 2.99 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.41 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H).

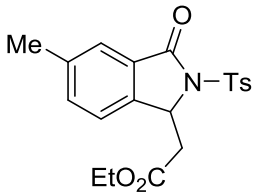
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.5 (C_q), 164.0 (C_q), 147.7 (C_q), 145.5 (C_q), 135.6 (C_q), 134.9 (CH), 133.0 (C_q), 131.0 (CH), 129.8 (CH), 128.7 (CH), 125.7 (C_q), 121.5 (CH), 61.2 (CH_2), 57.1 (CH), 39.1 (CH_2), 21.8 (CH_3), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3091, 2982, 1728, 1600, 1498, 1380, 1363, 1210, 1118, 816 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 467 (13) [M+K$^+$], 430 (91) [M+Na$^+$], 408 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{19}ClNO_5S$, [M+H$^+$] 408.0667, found 408.0662.

Synthesis of Ethyl 2-(5-methyl-3-oxo-2-tosylisondolin-1-yl)acetate 136hc



The general procedure **F** was followed using 3-methyl-*N*-tosylbenzamide (**135h**) (289.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136hc** (244 mg, 63%) as a colorless solid.

M.r.: 154–156 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.56 (s, 1H), 7.44−7.29 (m, 4H), 5.55 (dd, *J* = 8.1, 3.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.52 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.90 (dd, *J* = 16.5, 8.1 Hz, 1H), 2.41 (s, 3H), 2.29 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

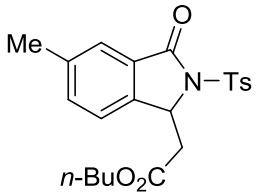
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.0 (C_q), 166.6 (C_q), 145.3 (C_q), 142.8 (C_q), 139.6 (C_q), 135.9 (C_q), 135.5 (CH), 129.7 (CH), 129.5 (C_q), 128.4 (CH), 125.1 (CH), 122.9 (CH), 61.1 (CH_2), 58.4 (CH), 39.6 (CH_2), 21.8 (CH_3), 21.4 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2976, 2943, 1725, 1355, 1302, 1165, 1151, 1082, 816, 659 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 426 (90) [M+K$^+$], 410 (77) [M+Na$^+$], 388 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}NO_5S$, [M+H$^+$] 388.1213, found 388.1213.

Synthesis of *n*-Butyl 2-(5-methyl-3-oxo-2-tosylindolin-1-yl)acetate 136he



The general procedure **F** was followed using 3-methyl-*N*-tosylbenzamide (**135h**) (289.3 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136he** (248 mg, 60%) as a colorless solid.

M.p.: 106 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.44−7.29 (m, 4H), 5.54 (dd, J = 8.1, 3.4 Hz, 1H), 4.02 (td, J = 6.7, 0.9 Hz, 2H), 3.52 (dd, J = 16.5, 3.4 Hz, 1H), 2.91 (dd, J = 16.5, 8.1 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 1.63−1.41 (m, 2H), 1.38−1.15 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).

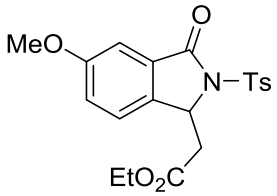
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.0 (C_q), 166.6 (C_q), 145.2 (C_q), 142.8 (C_q), 139.6 (C_q), 135.9 (C_q), 135.5 (CH), 129.7 (CH), 129.5 (C_q), 128.4 (CH), 125.0 (CH), 122.9 (CH), 65.0 (CH_2), 58.4 (CH), 39.5 (CH_2), 30.5 (CH_2), 21.8 (CH_3), 21.3 (CH_3), 19.1 (CH_2), 13.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2962, 1722, 1353, 1309, 1161, 1090, 811, 691, 576, 544 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 454 (100) [M+K$^+$], 438 (74) [M+Na$^+$], 416 (74) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{22}H_{26}NO_5S$, [M+H$^+$] 416.1526, found 416.1528.

Synthesis of Ethyl 2-(5-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136ic

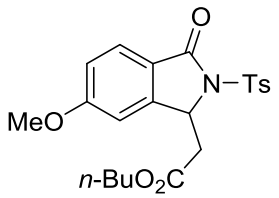


The general procedure **F** was followed using 3-methoxy-*N*-tosylbenzamide (**135i**) (305.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136ic** (219 mg, 51%) as a colorless solid.

M.r.: 130–132 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.40−7.29 (m, 3H), 7.22−7.09 (m, 2H), 5.52 (dd, J = 8.3, 3.3 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.52 (dd, J = 16.5, 3.4 Hz, 1H), 2.88 (dd, J = 16.5, 8.2 Hz, 1H), 2.41 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 166.4 (C_q), 160.6 (C_q), 145.2 (C_q), 137.7 (C_q), 135.8 (C_q), 130.6 (C_q), 129.7 (CH), 128.4 (CH), 124.1 (CH), 122.9 (CH), 107.0 (CH), 61.1 (CH_2), 58.3 (CH), 55.9 (CH_3) 39.6 (CH_2), 21.9 (CH_3), 14.3 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2982, 1725, 1496, 1360, 1295, 1164, 1164, 1014, 800, 779 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 442 (86) [M+K$^+$], 426 (100) [M+Na$^+$], 404 (71) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}NO_6S$, [M+H$^+$] 404.1162, found 404.1162.

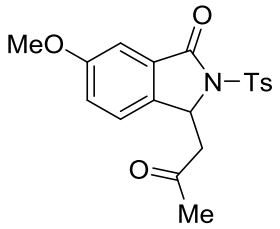
Synthesis of *n*-Butyl 2-(5-methoxy-3-oxo-2-tosylindolin-1-yl)acetate 136ie



The general procedure **F** was followed using 3-methoxy-*N*-tosylbenzamide (**135i**) (305.3 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136ie** (263 mg, 61%) as a colorless solid.

M.p.: 106 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.4 Hz, 2H), 7.40−7.29 (m, 3H), 7.23−7.06 (m, 2H), 5.52 (ddd, J = 8.2, 3.4, 0.8 Hz, 1H), 4.02 (td, J = 6.7, 0.9 Hz, 2H), 3.53 (dd, J = 16.5, 3.4 Hz, 1H), 2.89 (dd, J = 16.5, 8.2 Hz, 1H), 2.41 (s, 3H), 1.57−1.42 (m, 2H), 1.38−1.15 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.0 (C_q), 166.5 (C_q), 160.7 (C_q), 145.3 (C_q), 137.8 (C_q), 135.8 (C_q), 130.7 (C_q), 129.7 (CH), 128.4 (CH), 124.2 (CH), 122.9 (CH), 107.1 (CH), 65.0 (CH_2), 58.2 (CH), 55.8 (CH_3), 39.5 (CH_2), 30.5 (CH_2) 21.8 (CH_3), 19.1 (CH_3), 13.5 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2960, 1725, 1624, 1597, 1495, 1463, 1357, 1322, 1281, 1164 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 470 (34) [M+K$^+$], 454 (26) [M+Na$^+$], 432 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{22}H_{26}NO_6S$, [M+H$^+$] 432.1475, found 432.1475.

Synthesis of 6-Methoxy-3-(2-oxopropyl)-2-tosylisoindolin-1-one 136ij



The general procedure **F** was followed using 3-methoxy-*N*-tosylbenzamide (**135i**) (305.3 mg, 1.00 mmol), methyl vinylketone (**17j**) (67.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136ij** (102 mg, 27%) as a colorless solid.

M.r.: 170–172 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 2H), 7.36−7.26 (m, 3H), 7.20−7.03 (m, 2H), 5.58 (ddd, J = 9.0, 2.9, 0.7 Hz, 1H), 3.83 (dd, J = 18.1, 3.0 Hz, 2H), 3.79 (s, 3H), 2.87 (dd, J = 18.0, 9.0 Hz, 1H), 2.41 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H).

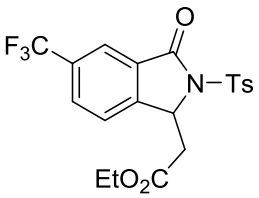
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 205.7 (C_q), 166.6 (C_q), 160.6 (C_q), 145.4 (C_q), 138.8 (C_q), 135.6 (C_q), 130.3 (C_q), 129.8 (CH), 128.4 (CH), 124.7 (CH), 123.1 (CH), 107.0 (CH), 57.8 (CH), 55.8 (CH_3), 49.2 (CH_2), 30.7 (CH_3), 21.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 3047, 3000, 2963, 2914, 2936, 1711, 1498, 1327, 1280, 1166 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 396 (97) [M+K$^+$], 391 (100) [M+Na$^+$], 374 (42) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{20}NO_5S$, [M+H$^+$] 374.1057, found 374.1057.

Synthesis of Ethyl 2-[3-oxo-2-tosyl-5-(trifluoromethyl)isoindolin-1-yl]acetate 136jc



The general procedure **F** was followed using *N*-tosyl-3-(trifluoromethyl)benzamide (**135j**) (171.5 mg, 0.50 mmol), ethyl acrylate (**17c**) (153.0 mg, 1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (219.0 mg, 1.05 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136jc** (172 mg, 78%) as a colorless solid.

M.r.: 127–129 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.98−7.96 (m, 3H), 7.86 (ddd, *J* = 8.1, 1.7, 0.7 Hz, 1H), 7.71−5.44 (m, 1H), 7.34 (dd, *J* = 8.0, 0.7 Hz, 2H), 5.64 (dd, *J* = 8.1, 3.3 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.55 (dd, *J* = 16.9, 3.3 Hz, 1H), 3.01 (dd, *J* = 16.9, 8.1 Hz, 1H), 2.42 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.5 (C_q), 165.1 (C_q), 148.5 (C_q), 145.7 (C_q), 135.5 (C_q), 132.1 ($^2J_{C\text{-}F}$ = 33.4 Hz, CH), 131.0 ($^3J_{C\text{-}F}$ = 3.5 Hz, CH), 130.4 (C_q), 129.9 (CH), 128.5 (CH), 124.2 ($^3J_{C\text{-}F}$ = 3.8 Hz, CH), 123.2 ($^1J_{C\text{-}F}$ = 274.5 Hz, C_q), 122.4 ($^3J_{C\text{-}F}$ = 7.0, 3.5 Hz, C_q) 61.3 (CH_2), 58.5 (CH), 38.8 (CH_2), 21.8 (CH_3), 14.1 (CH_3).

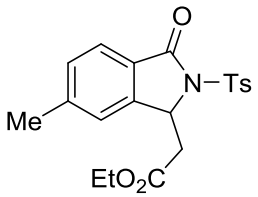
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -62.7 (s).

IR (ATR): $\tilde{\nu}$ = 2996, 1732, 1719, 1354, 1262, 1198, 1178, 1091, 1053, 1039 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 464 (70) [M+Na$^+$], 442 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{19}F_3NO_5S$, [M+H$^+$] 442.0931, found 442.0923.

Synthesis of Ethyl 2-(4-methyl-3-oxo-4-tosylisoindolin-1-yl)acetate 136kc



The general procedure **F** was followed using 4-methyl-*N*-tosylbenzamide (**135k**) (289.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136kc** (202 mg, 52%) as a colorless solid.

M.p.: 208 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.35−7.30 (m, 2H), 7.29−7.24 (m, 3H), 5.55 (dd, *J* = 8.1, 3.4 Hz, 1H), 4.17−4.02 (m, 2H), 3.51 (dd, *J* = 16.6, 3.5 Hz, 1H), 2.93 (dd, *J* = 16.6, 8.0 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

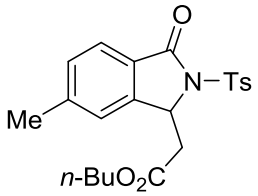
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.0 (C_q), 166.5 (C_q), 145.9 (C_q), 145.7 (C_q), 145.3 (C_q), 136.0 (C_q), 130.4 (CH), 129.8 (CH), 128.5 (CH), 126.8 (C_q), 124.9 (CH), 123.5 (CH), 65.1 (CH_2), 58.4 (CH), 39.6 (CH_2), 22.4 (CH_3), 21.8 (CH_3), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2966, 1715, 1617, 1354, 1168, 1087, 1033, 820, 761, 656 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 426 (100) [M+K$^+$], 410 (86) [M+Na$^+$], 388 (86) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}NO_5S$, [M+H$^+$] 388.1213, found 388.1214.

Synthesis of *n*-Butyl 2-(6-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136ke



The general procedure **F** was followed using 4-methyl-*N*-tosylbenzamide (**135k**) (289.3 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 1.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136k** (208 mg, 50%) as a colorless solid.

M.r.: 135–136 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.10−7.96 (m, 2H), 7.65 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.28−7.25 (m, 2H), 5.54 (dd, J = 8.1, 3.4 Hz, 1H), 4.11−3.89 (m, 2H), 3.52 (dd, J = 16.5, 3.4 Hz, 1H), 2.93 (dd, J = 16.5, 8.1 Hz, 1H), 2.43 (s, 3H), 1.54−1.45 (m, 2H), 1.34−1.22 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H).

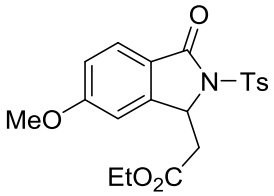
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.1 (C_q), 166.5 (C_q), 145.9 (C_q), 145.7 (C_q), 145.2 (C_q), 136.0 (C_q), 130.4 (CH), 129.7 (CH), 128.5 (CH), 126.8 (C_q), 124.9 (CH), 123.5 (CH), 65.1 (CH_2), 58.3 (CH), 39.5 (CH_2), 30.6 (CH_2), 22.3 (CH_3), 21.8 (CH_3), 19.2 (CH_2), 13.8 (CH_3).

IR (ATR): $\tilde{\nu}$ = 2960, 1719, 1618, 1355, 1339, 1170, 1091, 857, 838, 708 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 454 (16) [M+K$^+$], 438 (68) [M+Na$^+$], 416 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{22}H_{26}NO_5S$, [M+H$^+$] 416.1526, found 416.1529.

Synthesis of Ethyl 2-(6-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136lc

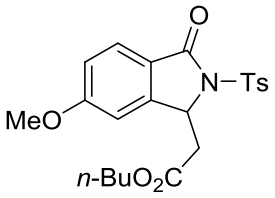


The general procedure **F** was followed using 4-methoxy-*N*-tosylbenzamide (**135l**) (305.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (13.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136lc** (223 mg, 52%) as a colorless solid.

M.r.: 186–189 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.00−6.92 (m, 2H), 5.53 (dd, J = 8.3, 3.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.54 (dd, J = 16.7, 3.4 Hz, 1H), 2.89 (dd, J = 16.6, 8.3 Hz, 1H), 2.41 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.1 (C_q), 166.1 (C_q), 164.9 (C_q), 148.1 (C_q), 145.2 (C_q), 136.0 (C_q), 129.7 (CH), 128.4 (CH), 126.8 (CH), 121.6 (C_q), 116.5 (CH), 107.5 (CH), 61.2 (CH_2), 58.1 (CH), 55.9 (CH_3) 39.7 (CH_2), 21.8 (CH_3), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2976, 2924, 2847, 1716, 1621, 1596, 1490, 1342, 1163, 1029 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 426 (100) [M+Na$^+$], 404 (55) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}NO_6S$, [M+H$^+$] 404.1156, found 404.1162.

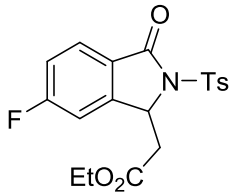
Synthesis of *n*-Butyl 2-(6-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136le



The general procedure **F** was followed using 4-methoxy-*N*-tosylbenzamide (**135l**) (305.3 mg, 1.00 mmol), *n*-butyl acrylate (**17e**) (138.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136le** (220 mg, 52%) as a colorless solid.

M.p.: 101 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.4 Hz, 2H), 7.72−7.59 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 6.97−6.91 (m, 2H), 5.51 (dd, J = 8.2, 3.3 Hz, 1H), 4.03 (t, J = 6.7 Hz, 2H), 3.83 (s, 3H), 3.52 (dd, J = 16.6, 3.4 Hz, 1H), 2.90 (dd, J = 16.7, 8.2 Hz, 1H), 1.58−1.41 (m, 2H), 1.36−1.21 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.1 (C_q), 166.1 (C_q), 164.9 (C_q), 148.0 (C_q), 145.1 (C_q), 136.0 (C_q), 129.7 (CH), 128.3 (CH), 126.6 (CH), 121.5 (C_q), 116.4 (CH), 107.4 (CH), 65.0 (CH_2), 58.1 (CH), 55.9 (CH_3) 39.6 (CH_2), 30.5 (CH_2), 21.7 (CH_3), 19.1 (CH_2), 14.2 (CH_3).
IR (ATR): $\tilde{\nu}$ = 2958, 1722, 1343, 1248, 1172, 1085, 1027, 863, 799, 761 cm^{-1}.
MS (ESI) *m/z* (relative intensity): 470 (69) [M+K$^+$], 454 (56) [M+Na$^+$], 432 (100) [M+H$^+$].
HR-MS (ESI) *m/z* calcd for $C_{22}H_{26}NO_6S$, [M+H$^+$] 432.1475, found 432.1475.

Synthesis of Ethyl 2-(6-fluoro-3-oxo-2-tosylisoindolin-1-yl)acetate 136mc



The general procedure **F** was followed using 4-fluoro-*N*-tosylbenzamide (**135m**) (293.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (114.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136mc** (191 mg, 49%) as a colorless solid.

M.r.: 188–191 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.77 (dd, J = 8.5, 5.0 Hz, 1H), 7.34 (dd, J = 8.6, 0.8 Hz, 2H), 7.24−7.11 (m, 2H), 5.64−5.44 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.56 (dd, J = 16.8, 3.2 Hz, 1H), 2.91 (dd, J = 16.8, 8.4 Hz, 1H), 2.42 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.8 (C_q), 166.7 ($^1J_{C\text{-}F}$ = 265.4 Hz, C_q), 165.4 (C_q), 148.1 ($^3J_{C\text{-}F}$ = 10.3 Hz, C_q), 145.5 (C_q), 135.7 (C_q), 129.8 (CH), 128.5 (CH), 127.5 ($^3J_{C\text{-}F}$ = 10.2 Hz, CH), 125.5 ($^4J_{C\text{-}F}$ = 2.1 Hz, C_q), 117.5 ($^2J_{C\text{-}F}$ = 23.7 Hz, CH), 110.9 ($^2J_{C\text{-}F}$ = 24.9 Hz, CH), 61.4 (CH_2), 58.1 ($^4J_{C\text{-}F}$ = 2.8 Hz, CH), 39.3 (CH_2), 21.8 (CH_3), 14.2 (CH_3).

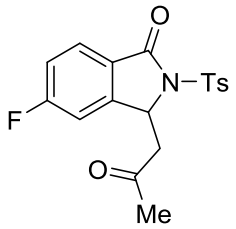
^{19}F-NMR (282 MHz, $CDCl_3$): δ = -101.7 (td, J = 8.5, 5.0 Hz).

IR (ATR): $\tilde{\nu}$ = 2977, 2938, 1731, 1605, 1480, 1362, 1171, 1086, 827, 679 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 430 (86) [M+K$^+$], 414 (71) [M+Na$^+$], 392 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{19}H_{19}FNO_5S$, [M+H$^+$] 392.0962, found 392.0962.

Synthesis of 5-Fluoro-3-(2-oxopropyl)-2-tosylisoindolin-1-one 136mj



The general procedure **F** was followed using 4-fluoro-*N*-tosylbenzamide (**135m**) (293.3 mg, 1.00 mmol), methyl vinylketone (**17j**) (67.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg,

5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136mj** (211 mg, 58%) as a colorless solid.

M.r.: 177–178 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.4 Hz, 2H), 7.74 (dd, *J* = 8.1, 5.0 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.18−7.08 (m, 2H), 7.18−7.08 (d, *J* = 7.6 Hz, 1H), 5.61 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.85 (dd, *J* = 18.3, 2.8 Hz, 1H), 2.91 (dd, *J* = 18.3, 9.1 Hz, 1H), 2.41 (s, 3H), 2.25 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 205.4 (C_q), 166.7 ($^1J_{C\text{-}F}$ = 256.1 Hz, C_q), 165.4 (C_q), 148.9 ($^3J_{C\text{-}F}$ = 10.3 Hz, C_q), 145.6 (C_q), 135.5 (C_q), 129.9 (CH), 128.4 (CH), 127.4 ($^3J_{C\text{-}F}$ = 10.2 Hz, CH), 125.1 ($^4J_{C\text{-}F}$ = 2.0 Hz, C_q), 117.4 ($^2J_{C\text{-}F}$ = 23.9 Hz, CH), 111.3 ($^1J_{C\text{-}F}$ = 25.0 Hz, CH), 58.0 (CH), 48.9 (CH_2), 30.5 (CH_3), 21.8 (CH_3).

^{19}F-NMR (282 MHz, $CDCl_3$): δ = -101.5 (td, *J* = 8.7, 5.1 Hz).

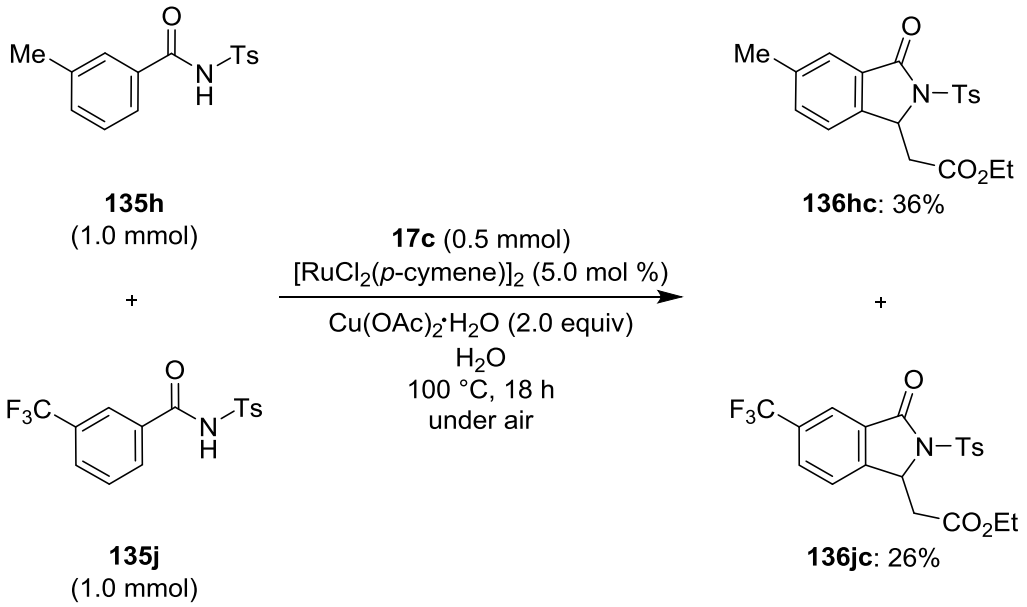
IR (ATR): $\tilde{\nu}$ = 2956, 2916, 1730, 1704, 1598, 1358, 1244, 1083, 1019, 877 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 384 (68) [M+Na$^+$], 362 (100) [M+H$^+$].

HR-MS (ESI) *m/z* calcd for $C_{18}H_{17}FNO_4S$, [M+H$^+$] 362.0857, found 362.0858.

5.3.9 Intermolecular Competition Experiment for the Ruthenium(II)-Catalyzed Synthesis of Isoindolinones

Competition Experiment between Tosylbenzamides 154h and 154j

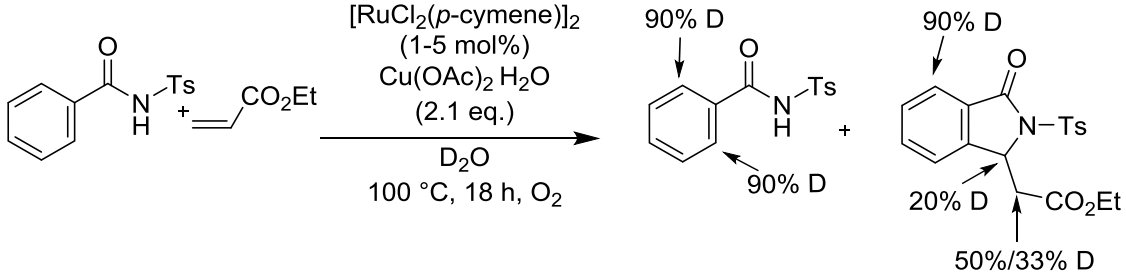


A mixture of 3-methyl-*N*-tosylbenzamide (**135h**) (289.0 mg, 1.00 mmol), *N*-tosyl-3-(trifluoromethyl)benzamide (**135j**) (343.3 mg, 1.00 mmol), ethyl acrylate (**17c**) (50.0 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (218.0 mg, 1.05 mmol) in H_2O (2.5 mL) was stirred at 100 °C for 18 h under air. At ambient temperature, the reaction mixture was diluted with sat. aq. NH_4Cl/NH_3 (1:1, 10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc 19/1) to yield **136hc** (68 mg, 36%) and **136jc** (56 mg, 26%).

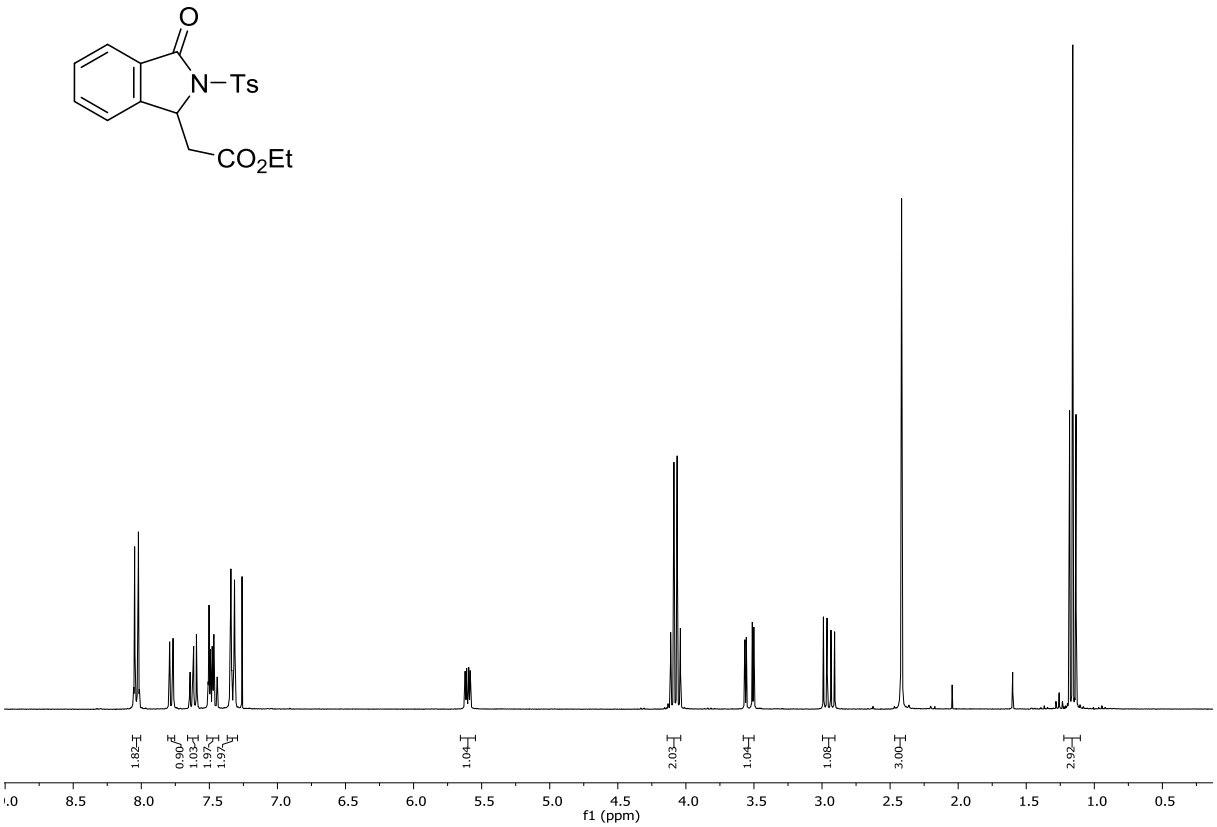
5.3.10 Mechanistic Studies on the Ruthenium(II)-Catalyzed Synthesis of Isoindolinones

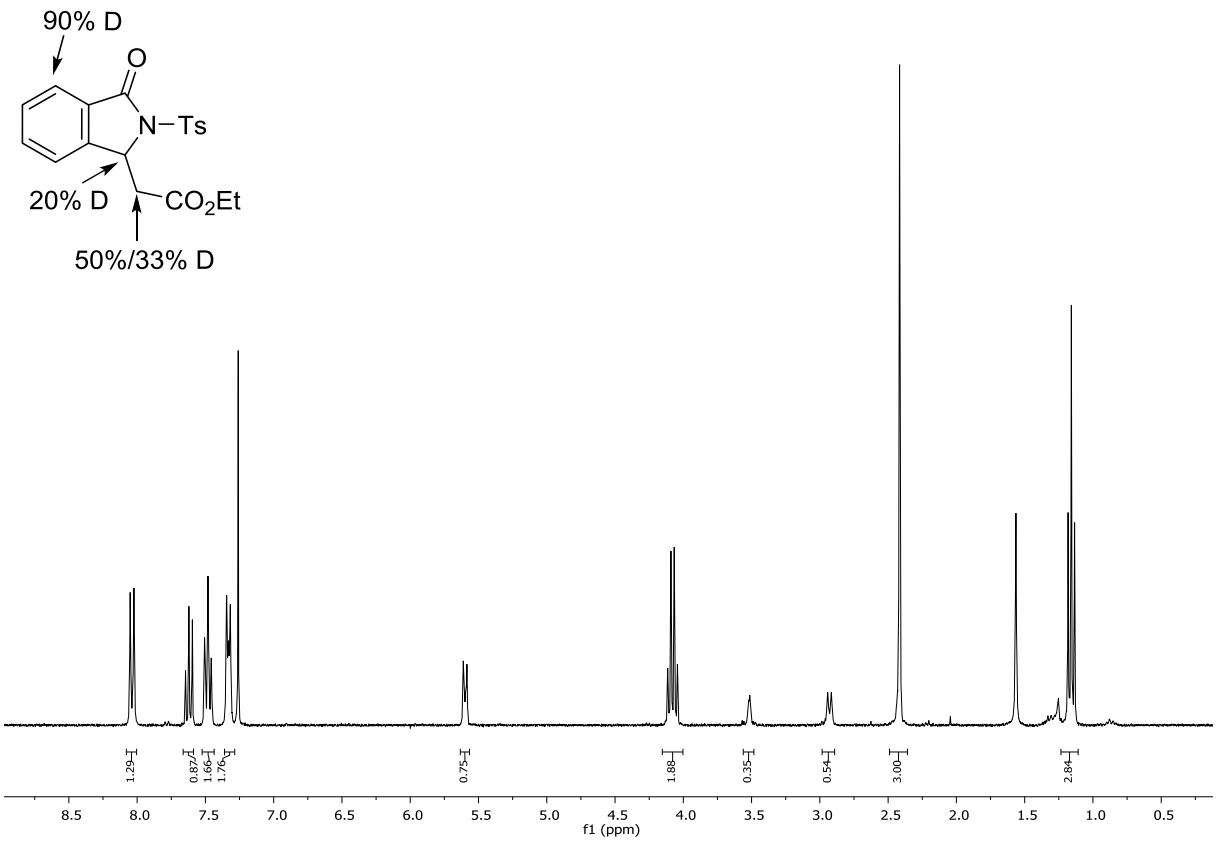
Ruthenium-Catalyced H/D Exchange with Substrate 135a with D_2O as the Cosolvent

The general procedure **F** was followed using 2-methyl-*N*-tosylbenzamide (**135a**) (2.98 mg, 1.00 mmol), ethyl acrylate (**17c**) (105.0 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ (419.3 mg, 2.10 mmol) in D_2O (5 mL) at 100 °C for 6 h. Purification by column chromatography (*n*-pentane/EtOAc 5.6/1) yielded $[D]_n$-**136ac** (212 mg, 68%) as a colorless solid and reisolated starting material $[D]_n$-**135a** (54 mg, 25%) as a colorless solid. The D-incorporation in $[D]_n$-**135a** and $[D]_n$-**136ac** in the *ortho*-position was estimated by ^{1}H-NMR spectroscopy.



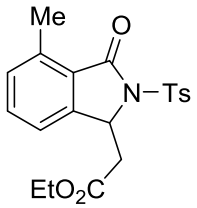
135a **17c** $[D]_n$-**135a** $[D]_n$-**136ac**


O
N−Ts
CO2Et
1.82
0.90
1.03
1.97
1.97
1.04
2.03
1.04
1.08
3.00
2.92
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


90% D
O
N−Ts
20% D
CO2Et
50%/33% D
1.29
0.87
1.66
1.76
0.75
1.88
0.35
0.54
3.00
2.84
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

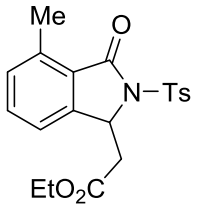
5.3.11 Ruthenium(II)-Catalyzed Synthesis of Isoindolinones using Oxygen as Sole Oxidant

Synthesis of Ethyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136bc



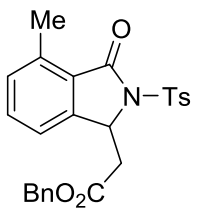
The general procedure **G** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136bc** (125 mg, 68%) as a colorless solid.
The spectral data are in accordance with those reported for **136bc** above (vide supra).

Synthesis of Ethyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136bc



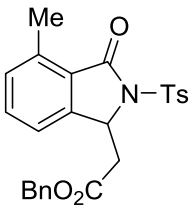
The general procedure **G** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and KOAc (49.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136bc** (158 mg, 86%) as a colorless solid.
The spectral data are in accordance with those reported for **136bc** above (vide supra).

Synthesis of Benzyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136bd



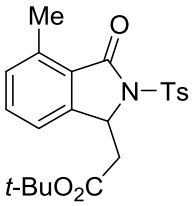
The general procedure **G** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), benzyl acrylate (**17d**) (380.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136bd** (179 mg, 80%) as a colorless solid.
The spectral data are in accordance with those reported for **136bd** above (vide supra).

Synthesis of Benzyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-yl)acetate 136bd



The general procedure **G** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), benzyl acrylate (**17d**) (380.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and KOAc (49.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136bd** (154 mg, 69%) as a colorless solid.
The spectral data are in accordance with those reported for **136bd** above (vide supra).

Synthesis of *tert*-Butyl 2-(4-methyl-3-oxo-2-tosylisondolin-1-yl)acetate 136bf



The general procedure **G** was followed using 3-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), *tert*-butyl acrylate (**17f**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (13.5 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136bf** (109 mg, 52%) as a colorless solid.

M.r.: 135–136 °C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.3 Hz, 2H), 7.50−7.42 (m, 1H), 7.34 (dd, J = 8.6, 0.7 Hz, 2H), 7.29 (dd, J = 7.7, 0.8 Hz, 2H), 5.50 (dd, J = 7.0, 3.5 Hz, 1H), 3.33 (dd, J = 16.4, 3.5 Hz, 1H), 3.03 (dd, J = 16.4, 7.0 Hz, 1H), 2.42 (s, 3H), 1.21 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.9 (C_q), 167.3 (C_q), 146.1 (C_q), 145.1 (C_q), 139.6 (C_q), 136.2 (C_q), 133.7 (CH), 131.0 (CH), 129.7 (CH), 128.6 (CH), 126.9 (C_q), 120.3 (CH), 81.7 (C_q), 57.7 (CH), 40.3 (CH_2), 27.7 (CH_3), 21.8 (CH_3), 17.7 (CH_3).

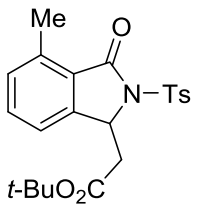
IR (ATR): $\tilde{\nu}$ = 2977, 1715, 1599, 1394, 1170, 1151, 1101, 799, 744, 700, 666, 574, 543 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 438 (57) [M+K$^+$], 433 (17) [M+Na$^+$], 416 (11) [M+H$^+$], 360 (100).

HR-MS (ESI) *m/z* calcd for $C_{22}H_{24}NO_5S$, [M-H$^+$] 414.1381, found 414.1363.

The spectral data are in accordance with those reported in the literature.[114b]

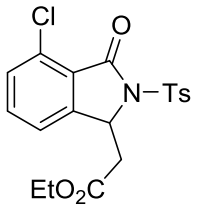
Synthesis of *tert*-Butyl 2-(4-methyl-3-oxo-2-tosylisondolin-1-yl)acetate 136bf



The general procedure **G** was followed using 3-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), *tert*-butyl acrylate (**17f**) (250.0 mg, 2.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (13.5 mg, 5.0 mol %) and KOAc (49.5 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136bf** (83 mg, 40%) as a colorless solid.

The spectral data are in accordance with those reported for **136bf** above (vide supra) and in the literature.[114b]

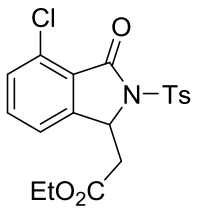
Synthesis of Ethyl 2-(4-chloro-3-oxo-2-tosylisoindolin-1-yl)acetate 136gc



The general procedure **G** was followed using 2-chloro-*N*-tosylbenzamide (**135g**) (154.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136gc** (110 mg, 54%) as a colorless solid.

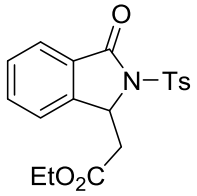
The spectral data are in accordance with those reported for **136gc** above (vide supra).

Synthesis of Ethyl 2-(4-chloro-3-oxo-2-tosylisoindolin-1-yl)acetate 136gc



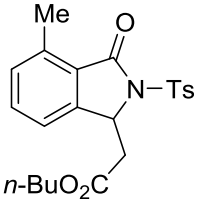
The general procedure **G** was followed using 2-chloro-*N*-tosylbenzamide (**135g**) (154.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and KOAc (49.5 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136gc** (157 mg, 77%) as a colorless solid.
The spectral data are in accordance with those reported for **136gc** above (vide supra).

Synthesis of Ethyl 2-(3-oxo-2-tosylisoindolin-1-yl)acetate 136ac



The general procedure **G** was followed using *N*-tosylbenzamide (**135a**) (138.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ac** (99 mg, 53%) as a colorless solid.
The spectral data are in accordance with those reported for **136ac** above (vide supra).

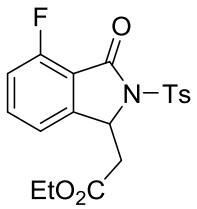
Synthesis of *n*-Butyl 2-(4-methyl-3-oxo-2-tosylisoindolin-1-1yl)acetate 136be



The general procedure **G** was followed using 2-methyl-*N*-tosylbenzamide (**135b**) (145.2 mg, 0.50 mmol), *n*-butyl acrylate (**17e**) (322.2 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg,

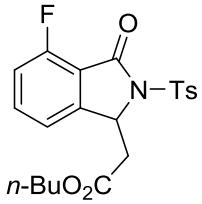
5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136be** (116 mg, 56%) as a colorless solid.
The spectral data are in accordance with those reported for **136be** above (vide supra).

Synthesis of Ethyl 2-(4-fluoro-3-oxo-2-tosylisoindolin-1-yl)acetate 136cc



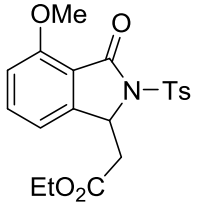
The general procedure **G** was followed using 2-fluoro-*N*-tosylbenzamide (**135c**) (147.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136cc** (166 mg, 85%) as a colorless solid.
The spectral data are in accordance with those reported for **136cc** above (vide supra).

Synthesis of *n*-Butyl 2-(4-fluoro-3-oxo-2-tosylisoindolin-1-yl)acetate 136ce



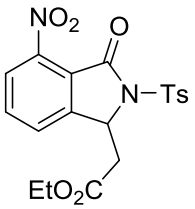
The general procedure **G** was followed using 2-fluoro-*N*-tosylbenzamide (**135c**) (146.7 mg, 0.50 mmol), *n*-butyl acrylate (**17e**) (322.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ce** (122 mg, 58%) as a colorless solid.
The spectral data are in accordance with those reported for **136ce** above (vide supra).

Synthesis of Ethyl 2-(4-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136dc



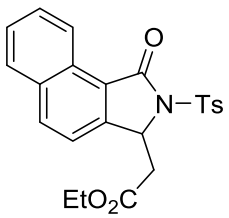
The general procedure **G** was followed using 2-methoxy-*N*-tosylbenzamide (**135d**) (152.7 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136dc** (105 mg, 52%) as a colorless solid.
The spectral data are in accordance with those reported for **136dc** above (vide supra).

Synthesis of Ethyl 2-(4-nitro-3-oxo-2-tosylisonidolin-1-yl)acetate 136fc



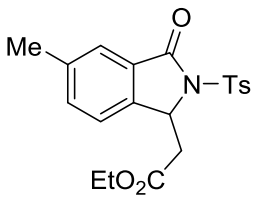
The general procedure **G** was followed using 2-nitro-*N*-tosylbenzamide (**135f**) (160.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136fc** (94 mg, 45%) as a colorless solid.
The spectral data are in accordance with those reported for **136fc** above (vide supra).

Synthesis of Ethyl 2-(1-oxo-2-tosyl-2,3-dihydro-1*H*-benzo[*e*]isoindol-3-yl)acetate 136ec



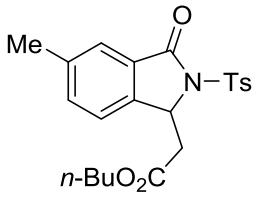
The general procedure **G** was followed using *N*-tosyl-1-naphtamide (**135e**) (162.7 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ec** (73 mg, 45%) as a colorless solid.
The spectral data are in accordance with those reported for **136ec** above (vide supra).

Synthesis of Ethyl 2-(5-methyl-3-oxo-2-tosylisondolin-1-yl)acetate 136hc



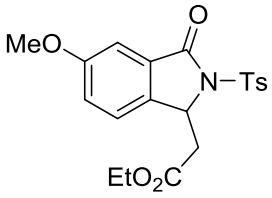
The general procedure **G** was followed using 3-methyl-*N*-tosylbenzamide (**135h**) (145.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 6/1) yielded **136hc** (126 mg, 65%) as a colorless solid.
The spectral data are in accordance with those reported for **136hc** above (vide supra).

Synthesis of *n*-Butyl 2-(5-methyl-3-oxo-2-tosylindolin-1-yl)acetate 136he



The general procedure **G** was followed using 3-methyl-*N*-tosylbenzamide (**135h**) (145.2 mg, 0.50 mmol), *n*-butyl acrylate (**17e**) (322.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136he** (98 mg, 47%) as a colorless solid.
The spectral data are in accordance with those reported for **136he** above (vide supra).

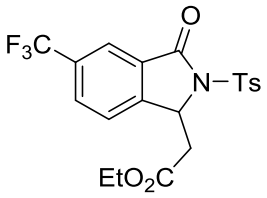
Synthesis of Ethyl 2-(5-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136ic



The general procedure **G** was followed using 3-methoxy-*N*-tosylbenzamide (**135i**) (152.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg,

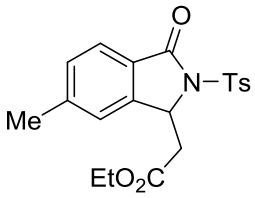
5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136ic** (121 mg, 60%) as a colorless solid.
The spectral data are in accordance with those reported for **136ic** above (vide supra).

Synthesis of Ethyl 2-[3-oxo-2-tosyl-5-(trifluoromethyl)isoindolin-1-yl]acetate 136jc



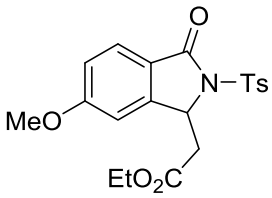
The general procedure **G** was followed using *N*-tosyl-3-(trifluoromethyl)benzamide (**135j**) (171.5 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136jc** (106 mg, 48%) as a colorless solid.
The spectral data are in accordance with those reported for **136jc** above (vide supra).

Synthesis of Ethyl 2-(4-methyl-3-oxo-4-tosylisoindolin-1-yl)acetate 136kc



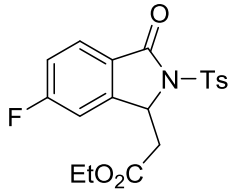
The general procedure **G** was followed using 4-methyl-*N*-tosylbenzamide (**135k**) (145.2 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136kc** (116 mg, 60%) as a colorless solid.
The spectral data are in accordance with those reported for **136kc** above (vide supra).

Synthesis of Ethyl 2-(6-methoxy-3-oxo-2-tosylisoindolin-1-yl)acetate 136lc



The general procedure **G** was followed using 4-methoxy-*N*-tosylbenzamide (**135l**) (152.7 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136lc** (121 mg, 60%) as a colorless solid.
The spectral data are in accordance with those reported for **136lc** above (vide supra).

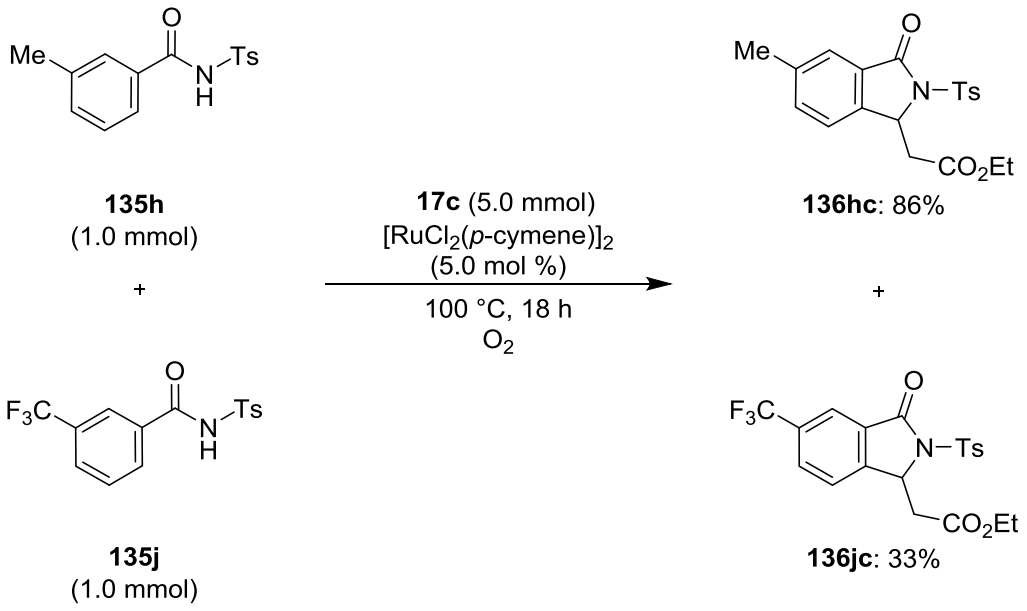
Synthesis of Ethyl 2-(6-fluoro-3-oxo-2-tosylisoindolin-1-yl)acetate 136mc



The general procedure **G** was followed using 4-fluoro-*N*-tosylbenzamide (**135m**) (146.7 mg, 0.50 mmol), ethyl acrylate (**17c**) (250.0 mg, 2.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %) and CsOAc (96.0 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc 4/1) yielded **136mc** (116 mg, 59%) as a colorless solid.
The spectral data are in accordance with those reported for **136mc** above (vide supra).

5.3.12 Intermolecular Competition Experiment for the Ruthenium(II)-Catalyzed Synthesis of Isoindolinones

Competition Experiment between Tosylbenzamides 135h and 135j



A suspension of 3-methyl-*N*-tosylbenzamide (**135h**) (145.0 mg, 0.50 mmol), *N*-tosyl-3-(trifluoromethyl)benzamide (**135j**) (171.0 mg, 0.50 mmol), ethyl acrylate (**17c**) (500.0 mg, 5.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 0.05 mmol, 5.0 mol %) and CsOAc (191.0 mg, 1.00 mmol, 1.0 equiv) was stirred at 100 °C for 18 h under an oxygen atmosphere. At ambient temperature, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (*n*-pentane/EtOAc) to yield **136hc** (167 mg, (86%) and **136jc** (72 mg, 33%).

Curriculum Vitae

Date of birth:	22 October, 1985 (Engelskirchen)
Nationality:	German

Scientific Education

12/2011 − present	Studies for a doctorate under supervision of Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry; Georg-August University Göttingen: ´Ruthenium-Catalyzed Synthesis of bioactive Compounds´
24.11.2011	Final examinations in chemistry (´Diplom´, grade ´very good´)
02/2011 − 11/2011	Diploma-thesis under supervision of Prof. Dr. Michael Famulok, Life & Medical Sciences Institute, Rheinische Friedrich-Wilhelms University Bonn: ´Characterization of Secin44: A Putative Cytohesin Inhibitor´
04/2008 − 02/2011	Advanced studies in chemistry at the Rheinische Friedrich-Wilhelms University Bonn
03.04.2008	Intermediate examination in chemistry (‘Vordiplom’, grade ‘good’)
10/2005 − 04/2008	Studies of chemistry at the Rheinische Friedrich-Wilhelms University Bonn

Education

08/1996 − 06/2005	Paul-Klee-Gymnasium Overath Abitur with grade 2.6 (Major subjects: History and Biology)
08/1992 − 06/1996	Primary school in Overath

Training

- Intercultural competency (Prof. S. Klein-Franke)
- Leadership competency (Stefanie Beckmann)

Teaching Experiences

Assistant for preparative practical and theoretics “Chemical laboratory for Medical Students” (06/2012 – 08/2014)

Conferences

10/2014	Poster presentation, Niedersächsisches Katalyse Symposium, Göttingen
03/2015	Poster presentation, Braunlage
07/2015	Poster presentation, 7. Göttinger Chemie-Forum 2015, Göttingen

Publications

C. Tirler, L. Ackermann, *"Ruthenium(II)-Catalyzed Cross-Dehydrogenative C−H Alkenylations by Triazole Assistance" Tetrahedron (Symposia in print)* **2015**, 4543-4551.